***In silico* Guided Drug Repurposing to Combat SARS-CoV-2 by Targeting M^{pro}, the key virus specific protease.**

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Abstract

The reemergence of SARS-CoV named, as SARS-CoV-2 has been highly infectious and able to infect a large population around the globe. The World Health Organization (WHO) has declared this SARS-CoV-2 associated Coronavirus Disease 2019 (COVID-19) as pandemic. SARS-CoV-2 genome is translated into polyproteins and has been processed by its protease enzymes. 3CLprotease is named as main protease (M^{pro}) enzyme which cleaves nsp4-nsp16. This crucial role of M^{pro} makes this enzyme a prime and promising antiviral target. The drug repurposing is a fast alternative method than the discovery of novel antiviral molecules. We have used high-throughput virtual screening approach to examine FDA approved LOPAC1280 library against M^{pro}. Primary screening have identified few potential drug molecule for the target among which 10 molecules were studied further. Molecular docking of selected molecules was done to detailed study about their binding energy and binding modes. Positively, Etoposide, BMS_195614, KT185, Idarubicin and WIN_62577 were found interacting with substrate binding pocket of M^{pro} with higher binding energy. These molecules are being advanced by our group for *in vitro* and *in vivo* testing to study the efficacy of identified drugs. As per our understanding, these molecules have the potential to efficiently interrupt the viral life cycle and may reduce or eliminate the expeditious outspreading of SARS-CoV-2.

Introduction

Recent mysterious outbreak of infectious agent in Wuhan, China has drawn huge attention of all scientific community of world. WHO have named this pneumonia like illness as COVID-19. Previously, epidemics of severe acute respiratory syndrome coronavirus (SARS-CoV) in Guangdong, China in 2003 and Middle East respiratory syndrome coronavirus (MERS-CoV) in 2013 have shown a high fatality rate. In both epidemics cases coronaviruses have shown cross-species transmission and infect humans as well as other vertebrates (Aleanizy et al., 2017; de Groot et al., 2013; Su et al., 2016; Wang et al., 2006; Zhong et al., 2003), In India, first coronavirus case confirmed on 30 January 2020 and till 23 march 2020 a total of 349 positive cases and 7 deaths have been confirmed in India (MOHFW, India). The occasional emergence of coronavirus has proved to be a substantial global threat to human lives.

According to International Committee on Taxonomy of Viruses (ICTV) coronavirus belongs to family *Coronaviridae*, subfamily *Orthocoronavirineae* and order *Nidovirales* which are

enveloped positive-sense single-stranded RNA virus (Lefkowitz et al., 2018; Masters, 2006). On the basis of phylogenetic relationships and genome structures, Coronavirinae subfamily have been classified into four genera - Alphacoronavirus, Betacoronavirus, Gammacoronavirus and Deltacoronavirus. The former two genera generally infects mammals whereas other two genera infects birds. SARS-CoV and MERS-CoV belongs to the Betacoronavirus genus (Woo et al., 2010).

The genome size of SARS-CoV-2 is ~30 kb with 12 open reading frames (ORFs). Genomic organization is in order 5'-replicase (rep)-spike (S)-envelope (E)-membrane (M)-nucleocapsid (N)-3' and short untranslated regions (Chan et al., 2020). The *rep* gene covers almost two-thirds of the genome and encodes two overlapping polyproteins pp1a and pp1ab using ORF1a and ORF1b. Papain-like protease and 3C-like protease cleaves the replicase polyprotein into 16 functional nonstructural proteins (nsp) that play a key role in transcription and replication of genome. (**Fig. 1**) (Cui et al., 2019; Song et al., 2019; Woo et al., 2010). Role of different non-structural proteins is as below (**Table 1**)

Downstream to *rep* gene sequence encodes four major structural proteins S, E, M and N which functions in formation of new virus progeny and their release (Rota et al., 2003). The S-protein are anchored protein over the envelope and interacts with host receptor by specific receptor-binding domain (RBD) (Wan et al., 2020) while E and M proteins are transmembrane proteins. The N binds with RNA at multiple sites and forms a helical nucleocapsid structure (Chang et al., 2014).

The 3C-like protease is also referred as M^{pro} or 3CL^{pro} as it functions as main protease enzyme. It cleaves at different sites in downstream polyproteins and forms individual proteins (Xia and Kang, 2011). It is a ~ 34-kDa protein, which have self-proteolytic activity to form a mature protease enzyme and function further (Yang et al., 2003). The monomer structure of M^{pro} have catalytic dyad of Cys-His at its active site whereas serine proteases have catalytic triad of Ser-His-Asp (Anand et al., 2002). The proteolysis activity of 3CL protease have shown Gln as most favorable residue at its P1 position (Chuck et al., 2010). Its mature structure consists of N-terminal domain I and domain II with chymotrypsin-like folds and a unique C-terminal domain III (Yang et al., 2003; Zhang et al., 2010).

Two monomers of M^{pro} forms its active structure as a homodimer by interaction between C-terminal domains (Zhong et al., 2009). Among the two monomer units only one is in correct confirmation and catalysis induced upon the dimerization of protein (Chen et al., 2006). 1-7 residues of N-terminal are termed as N-finger, which is accommodated between two monomer units (Yang et al., 2003). This N-finger is critical of dimerization of M^{pro} as well as formation of active dimeric form (Zhong et al., 2008). Further, a super active octamer form of M^{pro} has also been crystallized and studied which is highly active at low protein concentration (Zhang et al., 2010).

The substrate-binding pocket of M^{pro} have been specified by residues 41, 140, 142-145, 161, 163, 166 and 172 (Chen et al., 2006). His41 and Cys145 residues have been considered as prime residues for catalytic activity and remain conserved among *Coronaviridae* family

members (**Fig. 2**). H41A and C145A mutations completely abolishes protease activity (Huang et al., 2004). At present no efficacious therapy or vaccine is available against SARS-CoV-2. 3CL protease have major role in viral life cycle, which makes it a prime target to discover antivirals against SARS-CoV-2. In this study, we have targeted substrate-binding site of M^{pro} and repurposed few well-known FDA approved drugs against SARS-CoV-2 M^{pro}.

Materials and Methods

Virtual Screening:

To identify new potential antivirals against main protease (M^{pro}) of SARS-CoV-2 (PDB ID: 6LU7), we have performed virtual screening of pharmacologically active compounds using PyRx 0.8. All the drug-like molecules were retrieved from LOPAC¹²⁸⁰ drug library (Library of Pharmacologically Active Compounds, Sigma-Aldrich, St. Louis, MO) in SDF format. 1280 compounds were considered for high-throughput virtual screening. Energy minimization and conversion of all molecules into Autodock ligands (.pdbqt) format was done in PyRx 0.8. All the selected molecules were further undergone for screening against the probable binding sites of SARS-CoV-2 M^{pro} protein using PyRx 0.8 accompanied by AutoDock Vina. The grid centre points were set at X = -24.9165, Y = 12.3378, Z = 57.4364 and box dimensions were set as 48.30 Å × 69.97 Å × 60.87 Å with exhaustiveness 8. Top 10 molecules including Etoposide, BMS_195614, KT185, Idarubicin, GSK 121015A, WIN_62577, Eptifibatide_acetate, KT203, SB_202190 and GR_127935 were showing good binding efficacy and were selected for further analysis.

Molecular Docking:

Molecular docking of top 5 selected screened compounds were carried out using AutoDock 4.2.6. In docking procedure, all the water molecules were removed, non-polar hydrogens and Kollman charge (4.0) were added into the protein structure (PDB ID: 6LU7) using AutoDock MGL Tools 1.5.6. The protein was then saved in .pdbqt file format. The .pdbqt file format of top five hits ligands were retrieved from PyRx directory. The atomic potential grid map was calculated by AutoGrid 4 with a spacing of 0.316 Å and grid box dimensions were selected as (110 Å × 126 Å × 126 Å). The centre point co-ordinates set was X= -26.529, Y= 12.599 and Z= 58.965. Lamarckian Genetic Algorithm (GA) in combination of grid based energy evaluation method was used for docking. The number of total GA runs was increased 50 with maximum number of evaluations (250,000,000). Other docking parameters were set as default.

Results

Analysis of M^{pro} protease cleavage sites:

Comparative analysis of different *Coronavirinae* family members M^{pro} cleavage site residues using Multalin webserver (**Fig. 3**). Sequence of SARS CoV-2, SARS-CoV and MERS-CoV were retrieved from NCBI. Multiple sequence alignment showed that most of the residues are conserved among them as shown in Fig.2. We selected these peptides residues as substrate for the protein. Further these peptide sequence were designed using PyMOL and then docked against protease. Docking result suggest that the binding affinity of these peptide are lower than the selected screened compounds as shown in **Table 2**.

Virtual screening:

Potential antiviral compounds were extracted from LOPAC¹²⁸⁰ drug library in SDF format. 1280 compounds were considered for high throughput virtual screening with main protease (M^{pro}) of SARS-CoV-2 (PDB ID: 6LU7). Each ligand showed 9 different poses while screening through PyRx. Top 10 Molecules were selected by virtual screening on the basis of their binding affinity. For analysis, the molecules having highest binding energy were considered as top hits compounds. We selected top 10 compounds based on their 3binding energies that came in a range of -10.00 to -8.2 kcal/mol.

These selected screened molecules employed for docking with the M^{pro} to discover the potential inhibitor as shown in **Fig. 4**. Different length of peptide were also used as a substrate for comparison of the binding energy with the screened molecules. Pep1 is shown in **Fig. 5**.

Molecular docking:

Molecular docking of top 5 selected screened compounds were carried out using AutoDock 4.2.6. All the selected potential molecules fulfilling the five criteria of Lipinski rule. After the completion of docking, we found the binding energies of Etoposide, BMS_195614, KT185, Idarubicin, and WIN_62577 as (-10.23 kcal/mol), (-10.03 kcal/mol), (-9.5 kcal/mol), (-9.06 kcal/mol), and (-8.95 kcal/mol) and *in silico* inhibition constant (*ki*) were obtained as 31.86 nM, 44.5 nM, 106.5 nM, 229.43 nM, 273.66 nM. Molecular docking binding affinities of top 10 compounds are shown in **Table 3** whereas molecular docking binding affinities, *in-silico* inhibition constant and interactions analysis of top five molecules are shown in **Table 4**. The analysis were performed by using PyMOL software (**Fig. 4, 5, 6 & 7**) and LIGPLOT⁺ (**Fig. 8**) to further understand the interaction between the protein and the ligand molecules.

Etoposide possessed maximum numbers of hydrogen bonds involving Leu141, Gly143, Ser144, His163, Glu166 along with hydrophobic interaction His41, Phe140, Asn142, Cys145, His164, Met165, Leu167, Pro168, Asp187, Arg188, Gln189, Thr190 that displaying its affinity towards catalytic dyad (**Fig. 6, 7, & 8**). Ligand BMS_195614 interacted through hydrophobic residues only. Ligand KT185 interacted with Arg188 through hydrogen bond while other through hydrophobic bonds that include His41, Cys145, His164, Met165, Glu166, Leu167, Pro168, Gly170, Asp187, Gln189, Thr190 (**Fig. 6, 7, & 8**). Docked conformation of Idarubicin (-9.06 kcal/mol) and WIN_62577 (-8.95 kcal/mol) also displayed affinities towards the interacting residues by hydrogen and hydrophobic bonds.

Key interacting residues that play a significant role in all ligands along with other residues are His41, Phe140, Leu141, Asn142, Gly143, Cys145, His163, His164, Met165, Glu166, Leu167, Pro168, Asp187, Arg188, Gln189 and Thr190. The interaction clearly point out that these 5 screened drug molecules could potentially inhibit virus by inhibiting the main protease of SARS-CoV-2 by binding to the catalytic dyad of the protease which is responsible for its activity.

Further, different length of the peptide was also docked with the protease from which almost all peptide showed the docked score between -7.5 kcal/mol to -6.1 kcal/mol (**Table 2**). These

docking result demonstrated that the selected screened drug molecules showed better docking and binding affinity profiles. Thus, these drug molecules may be selected as possible protease inhibitors against SARS-CoV-2.

Discussion

M^{pro} (also termed as 3CLprotease) is the major proteolytic enzyme of SARS-CoV-2. As it cleaves nsp4-nsp16, this makes it a prime target for antiviral studies. Understanding of the proteolytic cleavage sites and their interaction properties with inhibitor molecules can pave new pathway in the direction of antiviral therapy development and combat against this pandemic. Till date COVID-19 have affected more than hundred countries of the world and there is no effective drug is available against it. So, to avoid the prolonged process of new drug molecules identification drug repurposing would prove to be of great benefit against SARS-CoV-2.

Non-structural polyprotein processing has been an important step in viral life-cycle which has mediated by M^{pro}. It interacts with substrate peptide chain by catalytic dyad (His41 and Cys145) present in substrate binding pocket (Chen et al., 2006). Structure based drug repurposing of FDA approved drugs is a rapid method to identify inhibitor molecules which can block the binding pocket of M^{pro}. We have successfully screened FDA approved LOPAC¹²⁸⁰ drug library against the the most probable binding site of M^{pro} that includes the interecting sites i.e; His41, Cys145, Phe140, Asn142, Gly143, Ser144, Tyr161, His163, Glu166, His172. The best top ten drugs compounds gives the binding energy in the range of -10.23 kcal/mol to -8.2 kcal/mol.

After the drug library screening, molecular docking studies enabled us to understand binding mode and crucial molecular interactions for potential drug molecules and M^{pro} substrate binding pocket. Intriguingly, all identified drug molecules are able to interact with His41 residue, which is key site for catalytic activity. The identified molecules and their roles have been listed in **Table 5**.

Our previous identification of KT185, KT203, BMS_195614, GSK1210151A, Eptifibatide acetate and GR127935 hydrochloride hydrate drug molecules have shown to inhibit the spike-ACE2 interaction at virus entry step (Choudhary et al., 2020). So these molecules can be better antiviral candidates because of their inhibitory action at virus-host cell receptor interaction as well as post-translation step of non-structural proteins.

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Tables -

Table 1 – Role of coronavirus non-structural proteins.

nsp	Function	Reference
nsp1	Translation inhibition and host mRNA degradation	Huang et al., 2011; Narayanan et al., 2008
nsp2	Host-and/or cell-specific roles with nsp1 and nsp3, Disrupt host signaling	Cornillez-Ty et al., 2009; Graham et al., 2006
nsp3	Papain-like protease, cleaves nsP1, 2 and 3	Lei et al., 2018
nsp4	Formation of double membrane vesicles (DMV), interaction with nsp3 for virus propagation	Beachboard et al., 2015; Sakai et al., 2017
nsp5	3CL proteinase, cleaves nsP4-16	Muramatsu et al., 2016; Ziebuhr et al., 2000
nsp6	DMV formation with nsp3, 4 and 6, Limits autophagosome size	Angelini et al., 2013; Cottam et al., 2014
nsp7	Co-factor for nsp12, interaction with nsp8 for de novo initiation and primer extension	Kirchdoerfer and Ward, 2019; te Velthuis et al., 2012
nsp8	Co-factor for nsp12, interacts with accessory protein	Kirchdoerfer and Ward, 2019; Kumar et al., 2007
nsp9	Single-stranded RNA binding protein, Interacts with nsp8	Egloff et al., 2004; Sutton et al., 2004
nsp10	Co-factor for nsp14 and nsp16	Bouvet et al., 2014
nsp11	Endoribonuclease in PRRSV*	Shi et al., 2016
nsp12	RNA dependent RNA polymerase activity with nsp7 and nsp8	Ahn et al., 2012; Kirchdoerfer and Ward, 2019; te Velthuis et al., 2010)
nsp13	Unwinding of duplex RNA, Helicase	Adedeji et al., 2012; Hao et al., 2017
nsp14	3'-5' exoribonuclease activity by interacting with nsp10	Bouvet et al., 2012; Minskaia et al., 2006
nsp15	Endoribonuclease, Protect viral dsRNA from host sensor detection	Bhardwaj et al., 2004; Deng et al., 2017
nsp16	2'-O-Methyltransferase activity with nsp10	Chen et al., 2011; Decroly et al., 2011

*PRRSV (Porcine Reproductive and Respiratory Syndrome Virus) is member of family *Arteriviridae* in order *Nidovirales*. In *Coronaviridae* its role has not been reported yet.

Table 2 - Representing different cleavage site between non-structural proteins in SARS-CoV-2. (-- Represents cleavage site)

Peptides	Cleavage site between non-structural protein	Amino acid residues	Binding Energy (kcal/mol)
Pep1	nsp4 - nsp5	AVLQ--SGFR	-7.5
Pep2	nsp5 – nsp6	VTFQ--SAVK	-6.5
Pep3	nsp6 – nsp7	ATVQ--SKMS	-6.0
Pep4	nsp7 – nsp8	ATLQ--AIAS	-6.4
Pep5	nsp8 – nsp9	VKLQ--NNEL	-6.3
Pep6	nsp9 – nsp10	VRLQ--AGNA	-6.8
Pep7	nsp10 – nsp12	PMLQ--SADA	-6.5
Pep8	nsp12 – nsp13	TVLQ--AVGA	-7.0
Pep9	nsp13 – nsp14	ATLQ--AENV	-6.1
Pep10	nsp14 – nsp15	TRLQ--SLEN	-6.1
Pep11	nsp15 – nsp16	PKLQ--SSQA	-6.2

Table 3 - Representation of binding energies of top 10 screened potential antiviral compounds of LOPAC¹²⁸⁰ library.

Ligand	Binding Energies (kcal/mol)
Etoposide	-10.23
BMS_195614	-10.03
KT185	-9.51
Idarubicin	-9.06
Win_62577	-8.95
Eptifibatide_acetate	-8.80
KT203	-8.60
LP_12_hydrochloride_hydrate	-8.60
SB_202190	-8.60
GR_127935	-8.60
GSK1210151A	-8.20

Table 4 - The values of binding energy, inhibition constant (*ki*), H-bond interactions & hydrophobic interactions obtained from docking of Etoposide, BMS_195614, KT185, Idarubicin, WIN_62577 into the catalytic site of M^{pro} (PDB ID: 6LU7) protein.

Compounds	<i>In silico</i> Inhibition Constant (<i>ki</i>)	Binding Energy (kcal/mol)	H-bond				Hydrophobic Interactions
			Residue No.	No. of Bonds	Molecules	Bond Length (Å ⁰)	
Etoposide	31.86 nM	-10.23	Leu141	1	O-O12	2.45	His41, Phe140, Asn142, Cys145, His164, Met165, Leu167, Pro168, Asp187, Arg188, Gln189, Thr190
			Gly143	1	N-O13	3.13	
			Ser144	2	OG-O12	2.77	
					N-O12	2.82	
			His163	1	NE2-O11	2.78	
			Glu166	1	O-O10	2.77	
BMS_195614	44.5 nM	-10.03					His41, Phe140, Leu141, Asn142, His163, His164, Met165, Glu166, Leu167, Pro168, Asp187, Arg188, Gln189
KT185	106.50 nM	-9.51	Arg188	1	O-N4	3.11	His41, Cys145, His164, Met165, Glu166, Leu167, Pro168, Gly170, Asp187, Gln189, Thr190
Idarubicin	229.43 nM	-9.06	Asn142	1	OD1-O3	2.75	His41, Tyr54, Phe140, Leu141, His164, Met165, Glu166, Leu167, Asp187, Arg188, Gln189
			Cys145	1	SG-O8	3.33	
			Pro168	1	O-O7	3.31	

WIN_62577	273.66 nM	-8.95	Glu166	1	OE1-N3	2.99	Thr25, Thr6, Leu27, His41, Met49, Leu141, Asn142, Gly143, Cys145, His164, Met165, Leu167, Pro168, Gln189
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Table 5 – Identified potential drug molecules against M^{pro} of SARS-CoV-2 and their role on RNA viruses.

S.No.	Identified drugs	Reported function of drug	Role on RNA viruses
1	KT185 KT203	Anti-inflammatory	<ul style="list-style-type: none"> • Inhibitor of ABHD6 receptor. • Decreases macrophage activation and exerts anti-inflammatory effect on lungs (Bottemanne et al., 2019; Hsu et al., 2013)
2	GR127935 hydrochloride hydrate	Controls vasoconstriction	<ul style="list-style-type: none"> • Antagonist of 5-HT1B/1D serotonin receptor. • Serotonin antagonists are potent entry inhibitors of Ebola and Marburg virus (Cheng et al., 2015)
3	Eptifibatide acetate	Lungs injury and inflammation	<ul style="list-style-type: none"> • Inhibitor of glycoprotein IIb/IIIa receptor responsible for platelet aggregation • Protects lungs from severe injury and inflammations induced by Influenza virus (Lê et al., 2015)
4	Etoposide	Anti-cancer drug	<ul style="list-style-type: none"> • Blocks cell cycle in S or G2 phase, inhibits Mdm2 synthesis
5	WIN_62577	Anti-inflammatory drug	<ul style="list-style-type: none"> • Tachykinin receptor (Substance P receptor) antagonist • Substance P is required for EMCV pathogenesis (Robinson et al., 2009) • Reduces bronchial smooth muscle constriction infected with RSV (Bost, 2004)
6	BMS_195614	Anti-cancer drug	<ul style="list-style-type: none"> • Inhibitor of Retinoic acid receptor • Inhibits Hepatitis B virus infection by decreasing hepatocyte permissiveness, through modulation of sodium taurocholate cotransporting polypeptide (NTCP) expression (Tsukuda et al., 2015)
7	GSK1210151A (I-BET151)	Bromodomain inhibitor	<ul style="list-style-type: none"> • Transcriptional repression of MYC (Chaidos et al., 2014) • MYC expression increased upon HCV induce β-catenin activation (Higgs et al., 2013)
8	LP-12-HCl- hydrate	Serotonin receptor agonist	<ul style="list-style-type: none"> • Agonist 5-Nonyloxytryptamine affects at Reovirus entry step (Mainou et al., 2015)

9	SB202190	p38 activation inhibitor	<ul style="list-style-type: none"> • Damages Zaire ebolavirus entry and reduce cytokine induction (Johnson et al., 2014) • Disrupts primary and secondary Host Gene Responses of Influenza virus (Börgeling et al., 2014)
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Figure Legends –

Fig. 1 – Schematic representation of SARS CoV-2 non-structural genes with boxes depicting their approximate protein size. Triangles are showing protease cleavage site of papain-like protease (black) and 3CL-protease (white).

Fig. 2 – Multiple Sequence Alignment (MSA) of binding pocket of M^{pro} of SARS-CoV-2, SARS-CoV and MERS-CoV showing consensus amino acids (His41, Cys145).

Fig. 3 - MSA of cleavage site between different non-structural proteins. (a) Pep1: between nsp4 - nsp5, (b) Pep2: between nsp5 - nsp6, (c) Pep3: between nsp6- nsp7, (d) Pep4: between nsp7 - nsp8, (e) Pep5: between nsp8 - nsp9, (f) Pep6: between nsp9 - nsp10, (g) Pep7: between nsp10 - nsp12, (h) Pep8: between nsp12 - nsp13, (i) Pep9: between nsp13 - nsp14, (j) Pep10: between nsp14 - nsp15 and (k) Pep11: between nsp15 - nsp16. Red color shows the conserved sequence.

Fig. 4 - Molecular docking interactions and orientations of top 10 screened ligands (top 5 compounds shown in green and remaining are in red) from LOPAC library and peptide (Pep1) shown in black color with binding pocket of M^{pro} (a) Ribbon diagram and (b) Surface structure. Yellow color sticks represents interacting residues of M^{pro}.

Fig. 5 - Molecular docking interactions and orientations of peptide (Pep1) with binding pocket of M^{pro} (a) Ribbon diagram and (b) Surface structure. Peptide is in black color, red represents catalytic dyad (His41 and Cys145) of M^{pro} and yellow color sticks represents interacting residues(Phe140, Asn142, Gly143, Ser144, Tyr161, His163, Glu166, His172) of M^{pro}.

Fig. 6 – Molecular docking interactions and orientations of top-hit screened ligands from LOPAC library with binding pocket of M^{pro}. (a) Etoposide, (b) BMS_195614, (c) KT 185, (d) Idarubicin and (e) WIN_62577. Cyan ribbons corresponds to residues of M^{pro}, simple presentation of ligand (red-green) with 60% transparency, yellow stick model represents hydrogen bonds and light blue stick model corresponds to hydrophobic interactions.

Fig. 7 – *In-silico* molecular docking surface structure of top-hit screened ligands from LOPAC library with binding pocket of M^{pro}. (a) Etoposide, (b) BMS_195614, (c) KT 185, (d) Idarubicin and (e) WIN_62577. M^{pro} residues are shown in marine with 20% transparency, hydrophobic residues are shown in green, hydrogen bonds are in red color and ligand residues are shown in orange with 20% transparency.

Fig. 8 – Schematic representation of interactions made by screened drug molecules with binding pocket of M^{pro} of SARS-CoV-2 upon analysis using Ligplot. (a) Etoposide, (b) BMS_195614, (c) KT 185, (d) Idarubicin and (e) WIN_62577. Ligands are colored and represented in purple color, hydrogen bonds are displayed in green dotted lines, red stellations represents hydrophobic interactions and residues of proteins are shown in brown color.