Approach towards drugs repurposing: Docking studies with multiple target proteins associated with SARS-CoV-2

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Abstract

The current pandemic outbreak of COVID-19 due to viral infections by SARS-CoV-2 is now become associated with severe commotion on global healthcare and economy. In this extreme situation when vaccine or drugs against COVID-19 are not available, the only quick and feasible therapeutic alternative would be the drug repurposing approach. In the present work, *in silico* screening of some antiviral and antiprotozoal drugs using Autodock docking tool was performed. Two known antiviral drugs sorivudine and noricumazole B are predicted to bind to the active site of the viral proteases namely cysteine like protease or 3CL protease (3CLpro) and papain like protease (PLpro) respectively with a highly favorable free energy of binding. Further, the promising molecules were subjected for checking their activity on other molecular targets like spike protein S1, RNA dependent RNA polymerase (RdRp) and angiotensin converting enzyme 2 (ACE2) receptor. But the compounds were found not effective on rest other molecular targets.

Key words: SARS-Cov-2; cysteine like protease inhibition; papain like protease inhibition; sorivudine; noricumazole B

1 Introduction

The novel coronavirus (COVID-19), a potential threat to human health causes severe acute respiratory syndrome (SARS-CoV-2). The virus which is thought to be originated from Wuhan, China has resulted global pandemic due to its rapid spreading. World Health Organization (WHO) declared this outbreak as international public health emergency. Currently, more than 7.3 million people are affected globally due to COVID-19 and the reported death toll is ~ 415000. This becomes a major challenge on healthcare along with a disastrous effect on the global economy. Under these circumstances, development of therapeutics for the treatment of SARS-CoV-2 infections seems to be extremely urgent to prevent possible viral transmissions. To discover potential therapies against this pandemic, several clinical trials and continuous efforts are being made. But unfortunately, till now suitable and approved vaccines or drugs are not available to mitigate SARS-CoV-2 infection. As the process to develop new antiviral drugs requires lot of time and effort, so repurposing of existing drug molecules could be an immediate alternative to combat the present situation.

Coronaviruses, the member of *Coronaviridae* family consists of four *genera* known as alpha, beta, gamma, and delta [1]. SARS-CoV-2 and two other viruses namely SARS-CoV and Middle East respiratory syndrome virus (MERS-CoV) are beta-coronaviruses [2]. SARS-CoV-2 genome is over 30 kb [3], which encodes both structural and non-structural proteins responsible for the viral assembly, viral replication and host-pathogen interactions. The major structural proteins in the virus include spike glycoprotein, membrane proteins, envelope proteins and nucleocapsid proteins [4]. Interactions between spike glycoproteins from SARS-CoV-2 and the receptors on the host cell surface (such as angiotensin converting enzyme 2 (ACE2) and serine protease TMPRSS2) assists the entry of viral genes into the host cells through fusion of viral membrane and host cell membrane [5]. Upon infection, viral genome encodes two long polyproteins namely

pp1a and pp1ab within the cell [6]. The polyprotein pp1ab also bears putative RNA-dependent RNA polymerase (RdRp) and RNA helicase activities [6, 7]. The viral protease chymotrypsin-like protease (3CLpro) also known as main protease cleaves the polyproteins at 11 different sites to form several nonstructural and functional proteins, which play active role in viral replication [8]. The papain like protease (PLpro) is also involved in this proteolytic process to assist replication of virus [9]. Hence, 3CLpro and PLpro can be considered as effective molecular targets to the drugs administered in the purpose to prevent the formation of functional proteins responsible for the replication event. Along with that, the spike protein, ACE2 receptor of spike protein and RdRp have also been explored as promising drug targets to combat SARS-CoV-2.

In the present work, computational approach has been used for fast repurposing of known drugs against SARS-CoV-2 through molecular docking with multiple target proteins mentioned above.

2. Methods

2.1. Preparation of the structures of small molecules and proteins for docking

Three dimensional structures (as .mol file) of 12 antiviral compounds and 5 antiprotozoal compounds and 5 different control drugs were collected from ChemSpider (http://www.chemspider.com/). Their energy and geometry were optimized using parametric method 3 (PM3) in *ArgusLab 4.0* (http://www.arguslab.com). The crystal structure of the proteins associated with SARS-CoV-2 namely 3CLpro (PDB ID: 6M0K), PLpro (PDB ID: 6W9C), RdRp (PDB ID: 6M71, in a complex with SARS-CoV-2 NSP7 and NSP 8,), spike protein S1 (PDB ID: 6W41, in complex with human antibody) and ACE2 (PDB ID: 6LZG, in a complex with spike glycoprotein) were downloaded from Protein Data Bank (PDB). To refine

these protein structures, bound ligands and/or proteins and the crystallographic water molecules were removed from the structure.

2.2 Drug-likeliness studies

Lipinski's rule of five determines the drug likeliness of a compound based on the parameters that its molecular weight should be less than 500 Da, not more than 5 hydrogen bond donors, not more than 10 hydrogen bond acceptors and the *log P* value does not exceed 5. These parameters were calculated for the compounds by using *SWISSADME* server (www.swissadme.ch/index.php).

2.3 Molecular docking

Protein-ligand dockings were performed by using *Autodock 4.2*. Before docking, hydrogens were added, torsion angles were confirmed and Kollman charges were added to the protein structure. The grid boxes for the blind docking were created in such a way that the whole protein was trapped within that box. Further, Lamarckian Genetic Algorithm (LA) protocol was applied to perform the docking. The lowest energy docked conformation obtained from each docking was saved as .pdb file. That docked conformation of ligand was merged with the corresponding protein structure and then that merged structure was used for the analysis of protein-ligand interactions. Interacting residues of the proteins along with the types of interactions involved were identified using Protein-Ligand Interaction Profiler (https://projects.biotec.tu-dresden.de/plip-web/plip). Molecular visualization and rendering of the structures were done in *PyMol*.

The structures, reported pharmacological activities and Lipinski's rule parameters of our test compounds are mentioned in Supplementary materials Table S1.

3. Results and Discussion

To prevent massive outbreak of infections caused by SARS-CoV-2, a halt on its replication process may be targeted. To achieve that, inhibition of the proteolytic activity of 3CLpro can be set as a major objective as reported earlier [10]. The molecules were docked with both the prime proteases of SARS-CoV-2 namely 3CLpro and PLpro using *Autodock* for screening their potential. In addition to that, we had also docked some control drugs (remdesivir, lopinavir, ritonavir and ribavirin), which are under some clinical trials against SARS-Cov-2. The estimated free energy of binding obtained from *Autodock* for each compound with two proteases is listed in Table 1. We had also checked the drug likeliness parameters of these drug molecules (Supplementary materials Table S1). Except mycalamide A and noricumazole B, other drug molecules do not show any violation of Lipinski's rule of five.

Table 1: Docking results associated with the lowest energy docked conformation of the compounds with 3CLpro and PLpro

Sr. No.	Compound	Docking with 3CLpro		Docking with PLpro	
		Binding energy (kcal/mol)	Inhibition constant (μM)	Binding energy (kcal/mol)	Inhibition constant (μM)
1.	Nicotianamine	-0.50	433660	+1.19	-
2.	Mycalamide A	-2.65	11340	-3.07	5590
3.	Ingavirin	-5.02	209.13	-4.65	392.97
4.	**Noricumazole B**	**-6.92**	8.43	**-6.59**	14.75
5.	Didanosine	-5.17	161.89	-4.89	259.29
6.	Trifluridine	-5.08	187.83	-4.39	609.78
7.	Cidofovir	-2.53	14100	-1.97	35760

8.	Acyclovir	-4.54	472.63	-3.94	1300
9.	Famciclovir	-4.65	390.66	-4.05	1080
10.	Ganciclovir	-5.69	67.24	-4.98	224.74
11.	**Sorivudine**	**-6.59**	14.67	**-7.39**	3.83
12.	Zidovudine	-5.53	89.10	-4.89	260.25
13.	Pyrimethamine	-5.77	59.38	-5.63	74.47
14.	Mefloquine	-6.14	31.53	-5.80	56.16
15.	Tinidazole	-5.14	169.82	-5.61	76.95
16.	Pentamidine	-5.84	51.98	-5.05	198.63
17.	**Artemether**	**-6.61**	14.40	**-6.23**	26.96
18.	Remdesivir	-4.35	644.64	-2.73	9910
19.	Ritonavir	-3.26	4060	-3.29	3860
20.	Lopinavir	-4.14	919.24	-4.51	497.85
21.	Ribavirin	-4.38	373.99	-3.95	1280

In Table 1, low Δ*G* values were estimated for the binding between 3CLpro and the antiviral compounds noricumazole B (-6.92 kcal/mol), sorivudine (-6.59 kcal/mol) and antiprotozoal compound artemether (-6.61 kcal/mol). Similarly, these three molecules have also been evolved with more favorable Δ*G* values for their binding with PLpro (-6.59, -7.39 and -6.23 kcal/mol for noricumazole B, sorivudine and artemether respectively). The estimated binding energies for other molecules mostly lie in the range of -4.5 to -5.7 kcal/mol and -4.0 to -5.6 kcal/mol in case of 3CLpro and PLpro respectively. The estimated Δ*G* values for the control drugs remdesevir, ritonavir, lopinavir and ribavirin are -4.35, -3.26, -4.14 and -4.38 kcal/mol with 3CLpro and -2.73, -3.29, -4.51 and -3.95 kcal/mol with PLpro respectively. Based on these values, noricumazole B, sorivudine and artemether seem to be promising inhibitors of 3CLpro and PLpro. We have further extended our study to trace the interactions playing in between 3CLpro and these three molecules. The major interacting residues of 3CLpro and PLpro involved in binding with these three drugs as well as with control drugs are mentioned in Table 2.

Table 2: Residues of 3CLpro and PLpro interacting with the compounds

Compound	Interacting residues of 3CLpro	Interacting residues of PLpro
Noricumazole B	*Hydrophobic interactions:* Ile 152, Tyr 154, Ile 249, Pro 293, Phe 294, Val 297 *Hydrogen bonding:* Tyr 154, Arg 298 *π-stacking:* Phe 294 *Salt bridge:* Arg 298	*Hydrophobic interactions:* Tyr 213, Glu 214, Glu 252, Tyr 305 *Hydrogen bonding:* Lys 217, Lys 254, Thr 257
Sorivudine	*Hydrophobic interactions:* Met 165 *Hydrogen bonding:* Glu 166, Thr 190, Gln 192	*Hydrophobic interactions:* Pro 59, Pro 68 *Hydrogen bonding:* Arg 65, Phe 79, Leu 80
Artemether	*Hydrophobic interactions:* Tyr 237, Tyr 239, Leu 272, Leu 286 *Hydrogen bonding:* Leu 287	*Hydrophobic interactions:* Lys 94, Tyr 95 *Hydrogen bonding:* Tyr 95 *Salt bridge:* Lys 94
Remdesivir	*Hydrogen bonding:* His 164, Gln 189, Thr 190, Gln 192	*Hydrophobic interactions:* Glu 161, Leu 162, Asp 164, Arg 166, Glu 167 *Hydrogen bonding:* Glu 161, Leu 162, Glu 167
Ritonavir	*Hydrophobic interactions:* Lys 5, Ala 7, Val 125, Tyr 126, Gln 127, Glu 288, Phe 291 *Hydrogen bonding:* Lys 5	*Hydrogen bonding:* Lys 91, Lys 94, Tyr 95
Lopinavir	*Hydrophobic interactions:* Tyr 239, Met 276, Ala 285 *Hydrogen bonding:* Leu 271, Gly 278, Ala 285	*Hydrophobic interactions:* Leu 101, Gln 122, Thr 259, Lys 279 *Hydrogen bonding:* Arg 140
Ribavirin	*Hydrogen bonding:* Ile 152, Tyr 154, Arg 298	*Hydrophobic interactions:* Leu 162, Pro 248, Tyr 264, Tyr 268, Gln 269 *Hydrogen bonding:* Lys 157, Gly 163, Asp 164, Glu 167, Asn 267

These residues interact with the molecules using different non-covalent forces such as hydrogen-bonding, hydrophobic, π-stacking, salt bridge interactions etc. The substrate binding site of 3CLpro is constituted by the residues Thr 25, Thr 26, His 41, Met 49, Gly 143, Cys 145, Glu 166, Pro 168 etc. A recent report has revealed the role of two catalytic residues namely His 41 and Cys 145 along with some other residues like Gly 143, Cys 145, His 163, His 164, Glu 166,

Pro 168 and Gln 189 for effective design of suitable inhibitors with 3CLpro [11]. Importance of these residues for the design antiviral compounds as inhibitors of 3CLpro was also supported by another recent publication [12]. The lowest energy docked conformation was presented for sorivudine with 3CLpro (Fig. 1A) and noricumazole B with PLpro (Fig. 1B) along with the interacting residues. Among the three top-scoring compounds (in terms of binding energy with 3CLpro), only sorivudine (Fig. 1A) was found to be docked closely in the binding site of 3CLpro. The catalytic residues His 41 and Cys 145 are 4.04 and 4.14 Å away from sorivudine molecule. Therefore, based on the free energy of binding as obtained from blind docking, we have screened three molecules and out of them only sorivudine seems to be binding close to the enzymatic active site, which plays an important role in viral replication. The compound demonstrates an inhibitory potential on 3CL protease with micromolar inhibition constant (~15 μM). In case of four control drugs, the binding energies appeared less favorable as compared to sorivudine. It is also evident from Table 2 that, among those control drugs, only ribavirin is binding at the catalytic site of 3CLpro.

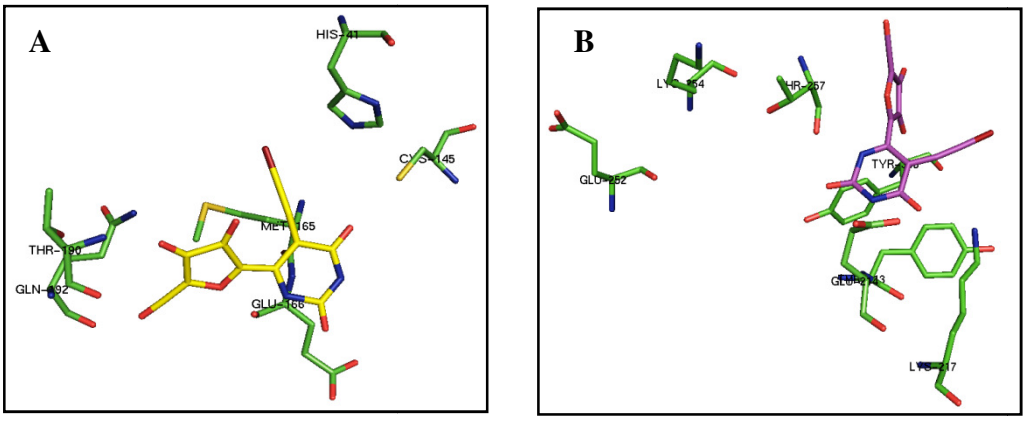

Fig. 1: Lowest energy docked conformation of (A) sorivudine (yellow) with 3CLpro, (B) noricumzole (magenta) with PLpro. Interacting protein residues are shown in green color.

We have also studied binding of 12 antiviral and 5 antiprotozoal drugs with the other protease PLpro of SARS-CoV-2. The binding of four control drugs (remdesivir, liponavir, ritonavir and ribavirin) with PLpro was also checked. In this protease, catalytic residues Cys 111 and His 272 (residue numbering according to the pdb file) are present in S1 pocket. But the substrate binding site is most probably the S3/S4 pockets, which are much more spacious than the S1/S2 pockets situated very close to the catalytic residues [13, 14]. The residues from Asp 164 to Glu 167, Met 208, Cys 217, Ala 246 to Pro 248, Tyr 264, Gly 266 to Gln 269, Gly 271, Tyr 273, Thr 301 and Asp 302 are present in the substrate binding region of PLpro [13, 14]. When we looked into the residues of PLpro interacting with these three molecules (Table 2), it was noticed that only noricumazole B is docked in the substrate binding site in the S3/S4 pockets (Fig. 1). This molecule is interacting closely with the residues of that pocket as mentioned above. Therefore, noricumazole B is expected to inhibit the proteolytic activity of PLpro as its binding in that region can inhibit the enzymatic activity of PLpro. Based on the promising results of sorivudine and noricumazole B on 3CLpro and PLpro respectively, we have extended our study with these three molecules for binding with other target proteins. The docking results are given in Table 3. The residues of spike protein S1, ACE2 receptor and RdRp interacting with these drugs are given in Table 4.

Table 3: Docking results associated with the lowest energy docked conformation of the compounds with spike protein S1, ACE2 receptor and RdRp

Sr. No.	Compound	Docking with Spike protein S1		Docking with ACE2		Docking with RdRp	
		Binding energy (kcal/mol)	Inhibition constant (μM)	Binding energy (kcal/mol)	Inhibition constant (μM)	Binding energy (kcal/mol)	Inhibition constant (μM)
1.	Noricumazole B	-8.18	1.01	-8.28	0.856	-7.17	5.52
2.	Sorivudine	-6.82	10.07	-7.59	2.73	-5.91	46.77

3.	Artemether	-7.47	3.34	-6.11	33.30	-6.44	18.96
4.	Remdesivir	NP	NP	NP	NP	-3.52	2630
5.	Ritonavir	NP	NP	NP	NP	NP	NP
6.	Lopinavir	NP	NP	NP	NP	NP	NP
7.	Ribavirin	-5.03	205.19	NP	NP	-3.32	3670
8.	Hydroxychloroquine	NP	NP	-5.77	58.63	NP	NP

NP - docking not performed

Table 4: Residues of spike protein S1, ACE2 receptor and RdRp interacting with three drug molecules

Compound	Residues of Spike protein S1 interacting with the molecule	Residues of ACE2 receptor interacting with the molecule	Residues of RdRp interacting with the molecule
Noricumazole B	*Hydrophobic interactions:* Pro 337, Phe 338, Glu 340, Phe 342, Leu 368 *Hydrogen bonding:* Ser 371, Ser 373 *π-stacking:* Phe 374, Trp 436	*Hydrophobic interactions:* Tyr 279, Asn 290, Ile 291, Pro 415, Glu 430, Phe 438, Lys 541 *Hydrogen bonding:* Thr 276, Tyr 279, Ser 280, Ile 291, Lys 441	*Hydrophobic interactions:* Phe 35, Ile 37, Lys 50, Val 71, Leu 119, Val 204, Thr 206, Asp 211 *Hydrogen bonding:* Tyr 38, Asn 39, Arg 116
Sorivudine	*Hydrophobic interactions:* Val 367 *Hydrogen bonding:* Asp 364, Tyr 365, Ser 371	*Hydrophobic interactions:* Pro 415 Phe 438 *Hydrogen bonding:* Ile 291	*Hydrophobic interactions:* Thr 319, Pro 461 *Hydrogen bonding:* Glu 350, Asn 628
Artemether	*Hydrophobic interactions:* Arg 457, Lys 458, Glu 471, Tyr 473, Pro 491 *Salt bridge:* Lys 458	*Hydrophobic interactions:* Phe 40, Leu 73, Leu 391, Asn 394, Lys 562 *Hydrogen bonding:* Arg 393, Asn 394	*Hydrophobic interactions:* Tyr 273, Leu 329 *Hydrogen bonding:* Val 330

A major hot spot is recently identified in the spike protein S1 of SARS-CoV-2 for its binding with ACE2 receptor [15]. This binding region in the spike protein is composed of Lys 417, Asn 487, Gln 493, Gln 498 and Tyr 505. The values of estimated free energy of binding with spike protein S1 are highly negative in case of these three molecules (Table 3). But the binding site for

noricumazole B, sorivudine and artemether (interacting residues enlisted in Table 4) in the spike protein is quite different than the predicted hot spot for receptor binding. So in this case, these molecules probably will not be effective to prevent the binding of the spike protein with its receptor on host cells. Similarly, the binding hotspot in ACE2 receptor is composed with Lys 31, His 34, Glu 35, Glu 37, Asp 38 and Try 83 [15]. In this case also, none of three molecules binds in that region of ACE2 to prevent the binding of spike protein S1 of SARS-CoV-2 with ACE2. In case of RdRp, two aspartic acid residues namely Asp 760 and Asp 761 (residue numbering as per pdb file) constitute the active site. From Table 4, it is also clear that these three molecules are not binding to the active site of RdRp also.

The design and development of new antiviral drugs is a time consuming and also involve complex processes. Hence, in the current context, repurposing of known drugs is an essential concept considering its cost effectiveness and ease of availability specifically at this point when the pandemic is posing as a global threat.

Conclusion

Using docking tool, known antiviral molecule sorivudine and noricumazole B were predicted to inhibit 3CLpro and PLpro of SARS-CoV-2 respectively, which are very important for viral replication. When these promising molecules were docked with other molecular targets associated with SARS-CoV-2 (spike protein S1, RNA dependent RNA polymerase and ACE2 receptor), it was observed that they are not binding to the active sites or hot spots of those targets. Therefore, sorivudine alone or a combination of sorivudine and noricumazole B may be administered to impede viral replication though the predicted drug likeliness of noricumazole B is not very much satisfactory. These observations are solely based on the results from blind

docking with protein molecules and that need to be further corroborated with experimental results to end up with a fruitful conclusion.

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Supplementary Materials

Approach towards drugs repurposing: Docking studies with multiple target proteins associated with SARS-CoV-2

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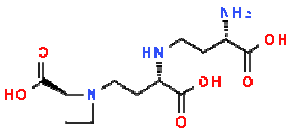
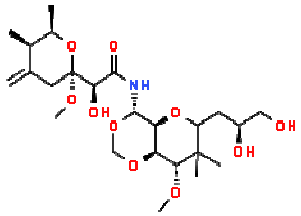
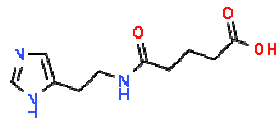
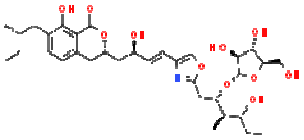
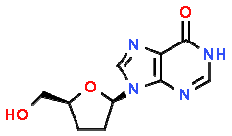
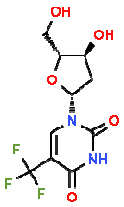
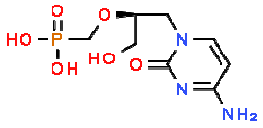
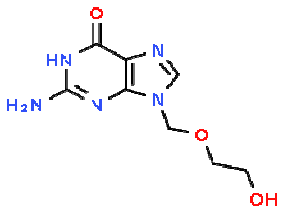
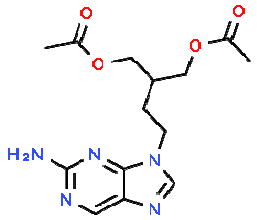
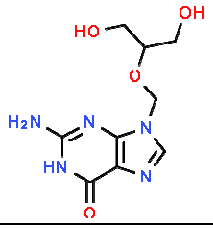
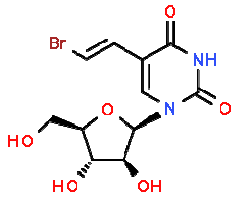
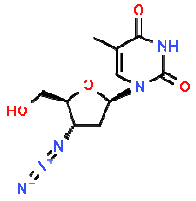
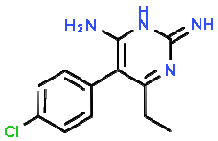
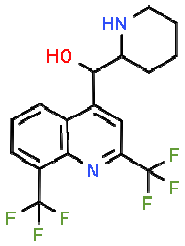
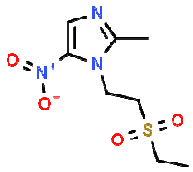
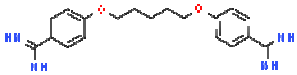
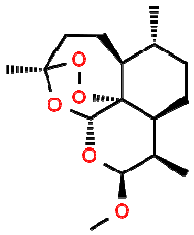
Sr. No.	Compound	Structure	Pharmaceutical activity			
22.	Nicotianamine		ACE2 inhibitor [1]	Molecular weight (<500)	303.31	8058557
				LogP (<5)	-3.38	
				H-Bond donor (≤5)	5	
				H-Bond acceptor (≤10)	9	
				Violation(s)	NIL	
23.	Mycalamide A		Polio virus, HSV-1, Influenza [2-4]	Molecular weight (<500)	503.58	30791722
				LogP (<5)	0.51	
				H-Bond donor (≤5)	4	
				H-Bond acceptor (≤10)	10	
				Violation(s)	1	
24.	Ingavirin		Influenza Virus A/H1N1 [5]	Molecular weight (<500)	225.24	8118269
				LogP (<5)	0.20	
				H-Bond donor (≤5)	3	
				H-Bond acceptor (≤10)	4	
				Violation(s)	NIL	
25.	Noricumazole B		HIV [6]	Molecular weight (<500)	633.73	28304049
				LogP (<5)	3.04	
				H-Bond donor (≤5)	6	
				H-Bond acceptor (≤10)	12	
				Violation(s)	3	

26.	Didanosine		HIV [7]	Molecular weight (<500)	236.23	45864
				LogP (<5)	0.24	
				H-Bond donor (≤5)	2	
				H-Bond acceptor (≤10)	5	
				Violation(s)	NIL	
27.	Trifluridine		HSV-1 [8]	Molecular weight (<500)	296.20	6020
				LogP (<5)	0.24	
				H-Bond donor (≤5)	3	
				H-Bond acceptor (≤10)	8	
				Violation(s)	NIL	
28.	Cidofovir		HCMV retinitis (AIDS patients) [9]	Molecular weight (<500)	279.17	54636
				LogP (<5)	-2.11	
				H-Bond donor (≤5)	4	
				H-Bond acceptor (≤10)	7	
				Violation(s)	NIL	

29.	Acyclovir		HSV, VZV [10]	Molecular weight (<500)	225.20	1945
				LogP (<5)	-0.91	
				H-Bond donor (≤5)	3	
				H-Bond acceptor (≤10)	5	
				Violation(s)	NIL	
30.	Famciclovir		HSV, VZV [11]	Molecular weight (<500)	321.33	3207
				LogP (<5)	0.75	
				H-Bond donor (≤5)	1	
				H-Bond acceptor (≤10)	7	
				Violation(s)	NIL	
31.	Ganciclovir		HCMV [12]	Molecular weight (<500)	255.23	3336
				LogP (<5)	-1.30	
				H-Bond donor (≤5)	4	
				H-Bond acceptor (≤10)	6	
				Violation(s)	NIL	
32.	Sorivudine		VZV [13]	Molecular weight (<500)	349.13	4445384
				LogP (<5)	-0.62	
				H-Bond donor (≤5)	4	
				H-Bond acceptor (≤10)	6	
				Violation(s)	3	
33.	Zidovudine		HIV [14]	Molecular weight (<500)	267.24	32555
				logP (<5)	-0.06	
				H-Bond donor (≤5)	2	
				H-Bond acceptor (≤10)	7	
				Violation(s)	NIL	
34.	Pyrimethamine		*P. falciparum* [15]	Molecular weight (<500)	248.71	4819
				logP (<5)	2.37	
				H-Bond donor (≤5)	2	
				H-Bond acceptor (≤10)	2	
				Violation(s)	NIL	
35.	Mefloquine		*P. falciparum* [15]	Molecular weight (<500)	378.31	3906
				logP (<5)	4.13	
				H-Bond donor (≤5)	2	
				H-Bond acceptor (≤10)	9	
				Violation(s)	NIL	

36.	Tinidazole		*G. intestinalis* [15]	Molecular weight (<500)	247.27	5279
				logP (<5)	0.07	
				H-Bond donor (≤5)	0	
				H-Bond acceptor (≤10)	5	
				Violation(s)	NIL	
37.	Pentamidine		*L. amazonensis* [15]	Molecular weight (<500)	340.42	4573
				logP (<5)	2.72	
				H-Bond donor (≤5)	4	
				H-Bond acceptor (≤10)	4	
				Violation(s)	NIL	
38.	Artemether		*P. falciparum* [15]	Molecular weight (<500)	298.37	62138
				logP (<5)	2.81	
				H-Bond donor (≤5)	0	
				H-Bond acceptor (≤10)	5	
				Violation(s)	NIL	

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