Binding repurposed drugs and aminothiourea derivatives to SARS-CoV-2 enzymes—a docking perspective

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Research Article

Keywords: SARS-CoV-2, docking analysis, aminothioureas

Posted Date: April 20th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-23928/v1>

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Abstract

Binding of over 20 approved drugs proposed for the repurposing for COVID-19 treatment and over 160 aminothiouras derivatives to SARS-CoV-2 enzymes which structures became available very recently have been evaluated using a few docking algorithms. These studies support potential effectiveness of homobarringtonine, chloroquine, rimcazone, and benserazine. From among studied aminothiouras thiadiazoles with pyrrol-derived substituents at the carbon atom, and *ortho*-hydroxyphenyl at the nitrogen atom are potential lead compounds for future drugs development.

Highlights

- Based on docking results to SARS-CoV-2 enzymes homobarringtonine, chloroquine, rimcazone, and benserazine are approved drugs with potential use in treatment of COVID-19 infection
- Pyrrol substituted thiadiazoles with *ortho* or *meta* substituted phenyl group attached to the nitrogen atom show strongest binding from among the studied aminothiouras

Introduction

With the outbreak of the SARS-CoV-21 devastating pandemic that claimed already lives of over 50000 people worldwide² the need for therapeutics is needed urgently. For the future prevention a few vaccine strategies are being tested. At the same time medicines that can be used in fighting the infection are being sought.

The family of coronaviruses is relatively well known due to the previous severe for humans epidemics of SARS³ and MERS.⁴ In haste search for medicines instantly available, repurposing of already approved drugs is carried out as the first line of defenses. This approach has been attempted during the MERS epidemic,⁵ and is also being tried currently.⁶ In the first of these studies an NIH library of over 700 compounds has been screened experimentally, identifying around 80 with the anti-coronavirus effect. The recent study concentrated on the interaction of the spike protein (S-protein) of the virus with the human ACE2 receptor, which is thought to be responsible for the viral recognition of host cells. By combining virtual high- throughput screening with ensemble docking of over 9000 compounds from the SWEETLAND library,⁷ and using COVID-19 S-protein (NCBI: YP_009724390.1) and human ACE2 receptor (PDB: 2AJF) as a template to generate the SARS-CoV-2 S-protein and ACE2 receptor complex model, around 80 compounds already in clinical use that should exhibit anti-coronavirus activity have identified.

While repurposing of compounds currently in medical use is the necessity for quick response to public health threat, in the long run drugs specific to this particular virus will be needed. With this aim in mind we have used the SARS-CoV-2 S-protein - ACE2 receptor complex model and its components to evaluate binding properties of thiosemicarbazides, thiadiazoles, and triazoles that we have studied for their anti-*Toxoplasma gondii*,^{8,9,10,11} antiviral,¹² antibacterial,^{13,14,15,16,17,18} anticancer,^{17,19,20,21}

anticonvulsant,^{22,23,24} analgesic,^{25,26} activities. Additionally, we have carried out docking to phosphatase (PDB: 6W02),²⁷ hydrolase

(PDB: 6W9C),²⁸ protease (PDB: 5RE5),²⁹ and endoribonuclease (PDB: 6W01)³⁰ SARS-CoV-2 enzymes that have been released recently at the Protein Data Bank.³¹ Our results point to three already identified in the previous studies currently used drugs and add as lead compounds for the future studies two compounds from thiosemicarbazides and their dehydrocyclic derivatives groups.

Material And Methods

Studied compounds

Approved drugs, selected as the best candidates in studies previously reported in literature,^{5,6} and compounds containing N-N-C(S)-N skeleton have been studied. The considered drugs are listed in Table 1 and referred to as series **L1** (best from reference 6) or **L2** (best from reference 5). Additionally, we have studied three drugs (labeled **A-1** - **A-3**). Chloroquine (**A-1**) was originally used as antiparasitic drug for treatment of malaria, but it has been shown to have also antiviral activity³² and has been currently recommended recently for use in SARS CoV-2 infection.^{33,34} Thus we have considered the other two which also are potent antiparasitic.

Among the compounds comprising the N-N-C(S)-N skeleton we have evaluated representatives of three classes of linear or cyclic molecules that have been studied in our laboratory in recent years for their inhibitory activity against a few enzymes. Their structures contain three main cores; linear carbonylthiosemicarbazide and its two cyclic derivatives: 1,3,4- thiadiazole and 1,2,4-triazole each decorated with two substituents. As the C-substituent one of the four five-member rings was used while the N-substituent was a benzene ring or its *ortho*, *meta*, or *para* substituted derivatives. All these components are collected in Table 2 where also partial codes for the fragments are provided (in bold). Thus, for example, compound code **ICpNO2** corresponds to 1-(4-methylimidazol-5-yl)-4-(4-nitrophenyl)thiosemicarbazide, illustrated in Fig. 1. This compound (together with **CCpNO2**, **CCml**, other **IC**) has been shown

to have no cytotoxicity in our recent studies on anti-*Toxoplasma gondii* activity (unpublished results). In total, 191 have been studied; 167 of the above compounds and 24 drugs.

Table 1. List of the approved drugs considered in current studies

eriodictyol (L1-1)	luteolin monoarabinose (L1-13)
dimethyl coclaurine (L1-2)	vildagliptin (L1-14)
vidarabine (L1-3)	carbazochrome (L1-15)
tazebactam (L1-4)	rimcazone (L2-1)
benserazine (L1-5)	triptolide (L2-2)
quercetin quercetin (L1-6)	fludarabine (L2-3)
nitrofurantoin (L1-7)	benzbromarone (L2-4)
protirelin (L1-8)	hexachlorophene (L2-5)
pyruvic acid isoniazid (L1-9)	homobarringtonine (L2-6)
pemirolast (L1-10)	chloroquine (A-1)
phenformin (L1-11)	sulfadiazine (A-2)
sapropterin (L1-12)	trimetoprim (A-3)

In silico evaluations

We have used the published model⁶ of the interface between the viral S-protein and the human ACE2 receptor that was constructed from COVID-19 S-protein (NCBI: YP_009724390.1) and human ACE2 receptor (PDB: 2AJF) as a template. The structure of this model has been recently confirmed experimentally.³⁵ For the selected compounds we have performed additional docking to other SARS-CoV-2 enzymes, which structures have become available very recently.²⁷⁻³⁰

A few docking algorithms have been tested. Initially, following literature data, Vina³⁶ docking program has been used. However, the scores obtained for strongest inhibitors were very close and not discriminating. We have, therefore switch to FlexX algorithm,³⁷ as implemented in the LeadIT platform.³⁸ The scoring function of this program did better job in

differentiation of binding affinities of studied compounds but showed some constrains, the most serious being the limit on the size of the acceptor, which precluded in some cases searches of the whole enzyme. SwissDock³⁹ at our hands also turned out not practical as only a single ligand per submission to the server was possible. We have therefore finally decided to continue with the ChemPLP algorithm⁴⁰ as implemented in the Gold program.⁴¹ It is also noteworthy that this algorithm has been considered as one of the best in most recent benchmark studies.⁴²

Table 2. List of structural fragments of compounds used in current studies

R ¹	core	R ²
2-methylfuran-3-yl (F)	carbonylthiosemicarbazide (C)
4-methyl-imidazol-5-yl (I)	1,3,4-thiadiazole (S)	R ³ = H , <i>ortho</i> , <i>meta</i> , or <i>para</i> : F , Cl , Br , I , OH , OMe , Me , NO₂
pyrrol-2-yl (P)	1,2,4-triazole-3-thione (T)
cyclopentyl (C)		

For the proteins and ligands preparation and visualization apart from those embedded in the docking programs, Hyperchem,⁴³ Gaussview,⁴⁴ Chimera,⁴⁵ and Mercury⁴⁶ were used.

Results And Discussion

The focus of the present studies was on the binding to virus S-protein, ACE2 human receptor, and their interface. The best 10 scores for each target, obtained using ChemPLP docking algorithm, are collected in the first 23 rows of Table 3. As can be seen four drugs already in clinical use; **L2-1**, **L2-6**, **A-1**, and **L1-5** exhibit the strongest binding. Among these rimcazole (**L2-1**) is the top one in binding to S-protein of the virus and second in binding to ACE2 receptor and their interface, although its strongest affinity is to the inside of the ACE2 receptor (with score of 64.37). Also, outstandingly strong binding to the interface is exhibited by chloroquine (**A-1**) most probably because of interactions with both proteins at the same time, as illustrated in Fig. 2. The source of the antiviral activity of in this case is, however, not clear because **A-1** binds even better to the complex than to individual proteins, acting rather like a binder than an inhibitor.

The analysis of structures containing the N-N-C(S)-N motif from the chemical point of view indicates that thiadiazoles with pyrrol substituent are among the top binding compounds, especially to the virus S-protein. The substituent attached to the nitrogen atom most frequently contains hydroxyl group in the *ortho* position.

Table 3. ChemPLP docking scores of studied compounds to S-protein, ACE2 receptor and their interface

compound	virus S-protein	human ACE2 receptor	interface
L2-1	59.78	55.60	56.76
L2-6	58.94	48.61	55.93
A1	51.94	51.48	66.29
PSoMe	49.05	47.45	52.09
FCpF	49.01	45.56	46.48
PSoF	49.01	47.68	51.83
PSmMe	48.98	49.64	50.57
PSmCl	48.73	48.87	50.63
PSoCl	48.46	47.48	50.24
PSmBr	48.05	49.56	50.69
L1-5	44.44	57.86	51.50
FSoOH	39.89	53.16	54.71
FSmOH	45.62	52.72	54.38
CCpNO2	41.24	52.6	53.25
FCmF	43.07	52.41	52.27
FCoOH	41.71	51.80	47.11
PCoNO2	44.41	51.73	48.48
FCmOH	46.07	51.68	50.24
PSpOH	42.04	48.04	53.16
PCoOH	45.80	52.02	53.09
FSoMe	41.29	49.44	52.66
FSpOMe	40.70	47.29	52.61
PSoNO2	44.16	48.76	52.61
L2-3	39.72	47.36	39.33
PToNO2	42.56	47.76	42.08
PTol	44.58	47.85	43.61
L1-14	45.62	49.08	44.89
ICoNO2	44.57	45.51	41.78

FCpOH	43.88	44.08	40.61
PToOMe	42.08	44.78	41.31
FSH	47.85	47.73	47.34
PTmNO2	44.46	45.55	43.07
L1-13	47.85	48.87	47.35
L2-2	39.34	38.78	37.31

In the bottom part of Table 3 we have ranked (by the maximum score difference) compounds which binding to the interface is weaker than to individual proteins, what would be expected for a typical competitive inhibitor. On the top of this list is again approved drug - fludarabine

(**L2-3**). These compounds, and the top 3 from the best binding list, have been docked to other SARS-CoV-2 proteins, which crystal structures have been solved recently. There are; ADP ribose phosphatase (PDB: 6W02), papain-like protease (PDB: 6W9C) and main protease (PDB: 5RE5), and endoribonuclease (PDB: 6W01). The results are collected in Table 4.

Table 4. Binding scores of selected compounds to SARS-CoV-2 proteins (PDB IDs given)

compound	6W01	6W02	6W9C	5RE5
L2-3	39.93	62.89	55.01	32.54
PToNO2	49.27	53.16	50.92	37.11
PTol	48.55	54.28	51.84	36.14
L1-14	43.3	70.47	62.78	34.61
ICoNO2	35.4	63.86	51.36	26.37
FCpOH	34.14	67.59	54.28	27.21
PToOMe	41.92	45.4	45.77	33.89
FSH	47.09	62.47	50.99	31.54
PTmNO2	49.6	54.97	54.79	32.42
L1-13	50.71	56.96	60.76	28.05
L2-2	40.44	42.37	37.46	25.95
L2-1	52.89	62.65	64.09	38.56
L2-6	43.47	65.55	62.96	29.04
L1-5	48.97	56.33	57.44	51.79
A1	49.52	73.2	61.78	34.82
A447	26.42	34.3	53.92	25.98

As can be seen again the currently used drugs, **L2-1** and **L1-5** exhibit the largest scores. Also, **A1** recently recommended for inclusion in the anticoronavirus treatment shows very high affinity to the phosphatase although this class of enzymes is generally considered undruggable.⁴⁸

Conclusions

Presented computational studies support recent observations that repurposing some drugs seems a promising way for COVID-19 treatment. Out of the studied drugs the most promising is homobarringtonine (**L2-6**) in agreement with recently suggested⁴⁹ its potential effectiveness of this drug in treating SARS-CoV-2 infection. Similar arguments can be claimed for chloroquine (**A1**). Furthermore, our studies point to rimcazone (**L2-1**), and benserazine (**L1-5**) as equally potential antivirus drugs especially because they seem to be nonspecific and strongly binding to a few virus enzymes.

From among studied compounds that are not approved for clinical use, it seems that thiadiazoles with pyrrol or its derivatives substituents at the carbon atom, and *ortho*-hydroxyphenyl at the nitrogen atom

might provide reasonable lead compounds for future drugs.

Declarations

Authors contributions statement

Both authors contributed to calculations, writing and reviewing the manuscript.

Competing interests

The authors declare no competing interests.

Acknowledgements

Financial support from the Foundation for Polish Science via the grant MAB PLUS/2019/11 is gratefully acknowledged.

Data Availability

The datasets generated and analysed during the current study are available from the corresponding author on reasonable request.

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Figures

Figure 1

Chemical structure of compound ICpN02

Figure 2

Chloroquine (A-1) bound to virus S-protein – human ACE2 receptor interface