Discovery of novel main protease inhibitors of SARS-CoV-2 using virtual screening and pharmacokinetic predictions

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Introduction

The major health concern is COVID-19 disease, which is caused by the SARS-CoV-2 virus. Curbing the spread of the virus has been challenging as it has various means of transmission including direct contact, via droplets, airborne, fomite, fecal-oral, bloodborne, sexual intercourse, ocular, mother-to-child, and animal-to-human. Therefore, the potential drugs have been urgently discovery for treatment of COVID-19

The main protease enzyme has been validated as a drug development target to stop SARS-CoV-2. Herein, we attempted to identify new promising main protease (M^{pro}) inhibitors from Specs database using virtual screening and binding mode

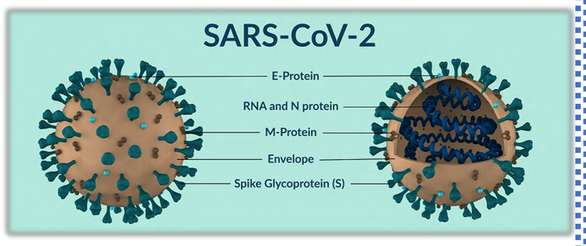

Figure 1. Structure of SARS-CoV-2

https://www.nsm.or.th/other-service/664-online-science/knowledge-inventory/sci-article/sci-article-science-museum/4649-sars-cov-2.html

Materials & Methods

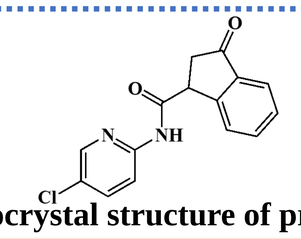

Figure 2. Cocrystal structure of protein PDB code 7P51

Zinc database
↓ 1000 compounds
Specs database
↓ 867 compounds
Drug-likeness properties
↓ 554 compounds
PAINS
↓ 539 compounds
SARS-balance prediction
↓ 93 compounds
3C-like protease (Human coronavirus) inhibitor
By PASS online prediction
↓ 90 compounds
Molecular Docking Calculations
Glide XP (PDB Code : 7P51)
↓ 24 compounds
Pharmacokinetic Properties (ADMET)

Figure 3. Virtual Screening workflow for the discovery of novel M^{pro} SARS-CoV-2 inhibitors

Conclusions

Three compounds, AA-504/07472048, AK-968/40046672 and AH-034/04906059 with good binding affinity and pharmacokinetic properties were obtained. Hydrogen bond interactions with Asn142 residue, pi-sigma interactions with Met165 residue and hydrophobic interactions with Met165, Gly143 and Leu27 residues in the SARS-CoV-2 M^{pro} binding site were found as crucial interactions. Based on pharmacokinetic properties predictions, these compounds were suitable to propose for biological assay evaluation and develop as anti-COVID-19 agents.

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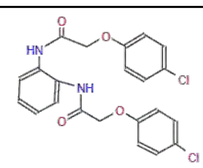
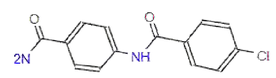
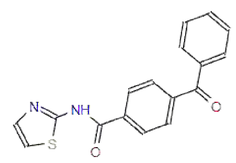
- Faculty of Science, Kasetsart University
- National Nanotechnology Center (NANOTEC)

Results

❑ Biological activity prediction and molecular docking studies

Table 1 SARS-balance prediction, 3C-like protease (human coronavirus) inhibitor using PASS online prediction and binding energy form molecular docking calculations.

Cpd.	Structures	SARS-balance prediction	3C-like protease (human coronavirus) inhibitor		Binding energy (kcal/mol)
			Pa	Pi	
AA-504/07472048		0.655	0.276	0.043	-8.274
AK-968/40046672		0.583	0.196	0.182	-7.141
AH-034/04906059		0.594	0.237	0.097	-7.126

❑ The binding mode and binding interaction of selected compounds in SARS-CoV-2 M^{pro} pocket.

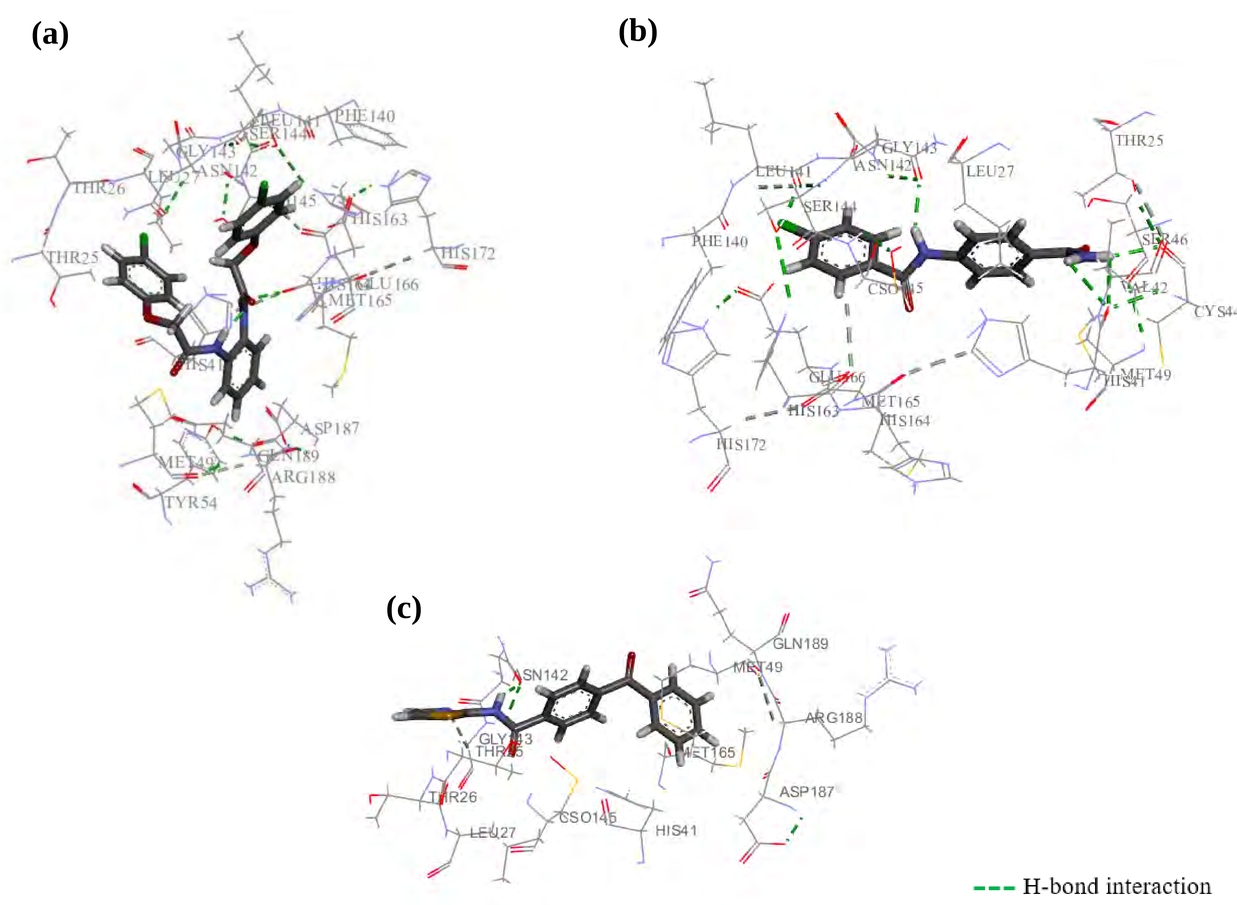


Figure 3 The binding mode of (a) AA-504/07472048, (b) AK-968/40046672 and (c) AH-034/04906059 in SARS-CoV-2 M^{pro} pocket.

❑ The pharmacokinetic properties (ADMET) prediction

Table 2 ADMET prediction of selected compounds

Specs ID	Caco2	Intestinal absorption (human)	BBB	CNS	CYP2D6 substrate	CYP3A4 substrate	CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	CYP2D6 inhibitor	CYP3A4 inhibitor	Total Clearance	Renal OCT2 substrate	AMES toxicity	hERG inhibitor	Oral Rat Acute Toxicity (LD_{50})	Hepato toxicity
AA-504/07472048	1.323	86.602	-0.703	-2.183	No	Yes	No	Yes	Yes	No	Yes	-0.298	No	No	Yes	2.057	No
AK-968/40046672	1.108	91.356	-0.065	-2.203	No	Yes	Yes	Yes	No	No	No	-0.42	No	Yes	No	1.985	No
AH-034/04906059	1.380	94.503	-0.17	-2.05	No	Yes	Yes	Yes	Yes	No	No	0.04	No	Yes	Yes	2.654	No

Caco2 > 0.90
high Caco2 permeability
Intestinal absorption (human) < 30%
is considered to be poorly adsorbed

BBB > 0.3
can readily cross the blood-brain
BBB < -1
poorly distributed to the brain

CNS > -2
can penetrate the Central Nervous System (CNS)
CNS < -3
unable to penetrate the CNS