Review of: "Discovery of S-217622, a Non-Covalent Oral SARS-CoV-2 3CL Protease Inhibitor Clinical Candidate for Treating COVID-19"

Malay Kumar Rana

Potential competing interests: The author(s) declared that no potential competing interests exist.

In the manuscript titled “Discovery of S-217622, a Non-Covalent Oral SARS-CoV-2 3CL Protease Inhibitor Clinical Candidate for Treating COVID-19”, a wide spectrum of work has been carried out: virtual screening, chemical syntheses, *in vitro* and *in vivo* studies to identify a non-peptidic therapeutic against SARS-CoV-2. Essentially, different variants of SARS-CoV-2 and other coronavirus members have been considered to demonstrate efficacy of the selected best 3CL Protease inhibitor (S-217622). In the manuscript, extensive and in-depth research has been conducted. The following comments may be considered for improving the manuscript:

1. The authors have taken three important pharmacophores for the structure based screening. But there is no pharmacophore chosen for interaction towards the catalytic residue Cys145 – any reason for this?.
2. The authors have explained very well about the interactions of different moieties with active site residues. It would be beneficial for future drug design against Mpro if the authors could shed light on the structure-activity relationship of the moieties.
3. What is the source of the in-house drug library? The detailed information can be helpful.
4. “Additionally, the antiviral efficacy of the 3CLpro inhibitor would likely be unaffected by and not induce mutations of the spike protein, which often occur in SARS-CoV-2 variants, because the 3CLpro and spike protein are distinct proteins encoded in different regions of the viral genome.” – The meaning is not very clear, suggest to rewrite it.
5. Instead of “P1 ligand”, I would prefer to use either “P1 moiety” or “P1 functional group”.