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

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

Reviewer

This manuscript summarizes the pivotal role of 3CLpro during life cycle of SARS-CoV-2 and the recent discovery of peptide-like 3CLpro inhibitors. Meanwhile, the study discovered the first non-peptidic, non-covalent SARS-CoV-2 3CLpro inhibitor, S-217622, which presents promising preclinical characterization. Virtual screening was firstly used to filter top-scoring compounds from the in-house library. Then, the hit compound was picked out for further straightforward multiparameter optimization so as to improve the fitness of pharmacophore and PK profile of the hit compound, gradually aimed with enzymatic assays, X-ray diffraction, cellular antiviral assays, in vivo SARS-CoV-2 infection experiments and systematical DMPK studies. The work of this paper integrally screened out the hit compound by virtual screening, as well as optimized the fitness of pharmacophore and PK profile of the hit compound based on irrefutable mechanisms, rendering a vitally ideal potent candidate. Thus, I recommend that this manuscript should be accepted by bioRxiv.

Some revision suggestions as follows,

1.Page 7, “giving some hit compounds with IC50 < 10 μM.”: More than one hit compound would show obvious inhibitory activity in enzymatic assay. The other effective compounds might be beyond hope of idiocratic mechanism or further structure modification. However, the undivided results of positive hit compounds are recommended to be presented as attachment in the paper, and superiority of choosing compound 1 is worth discussing.

2.Page 8, Fig 3: P1, 2 and 1’ of compound 1 were altered in a great extent. Please list inhibitory activities of the other reconstructed compounds during optimization, as well as discuss the diversity of these compounds in inhibitory activities.

3.Page 9, “the catalytic His41 was rotated”: Since S2 pocket recognizes P2 Leu/Met/Phe/Val, which might carry aromatic ring, resulting probable face-to-face π interaction with His41, it is remarkable to observe the interference caused by 3,4,5-trifluorobenzene moiety. Is this phenomenon particular for 3,4,5-trifluorobenzene moiety interacting with S2 pocket?

4.It is cheerful to discover a non-peptidic SARS-CoV-2 3CLpro inhibitor. Non-peptidic drugs have advantages in less intrinsic natural reactivity, higher membrane permeability and better metabolic stability. Nevertheless, the shortage of peptidic drug could be remedied with the help of pharmaceutics, and synthesis of peptidic drug is presumably more inexpensive than that of non-peptidic S-217622. The essential existence of non-peptidic S-217622 could be expounded more compellingly.