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COMPUTATIONAL APPROACH FOR IMPROVING OF KNOWN PERSPECTIVE SARS-COV-2 M^{PRO} INHIBITORS

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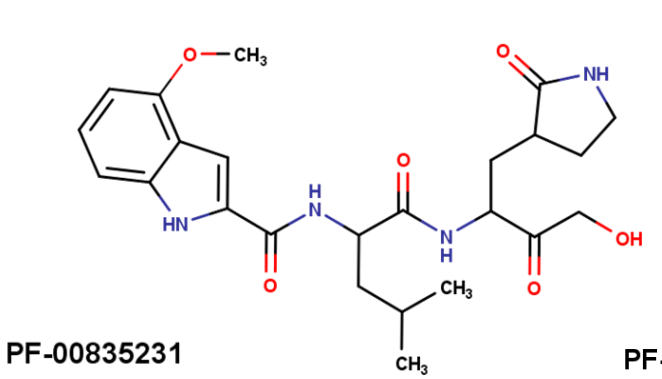
XXVIII Symposium on Bioinformatics and Computer-Aided Drug Discovery



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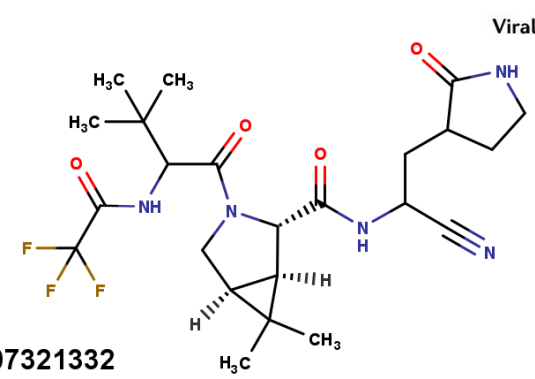

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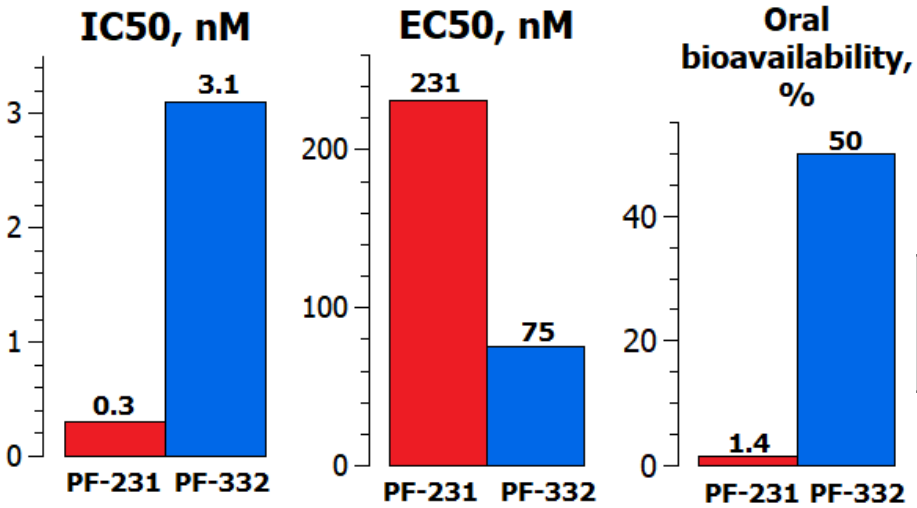

Owen D.R., Allerton C.M.N., Anderson A.S. et al. 2021. *Science*.

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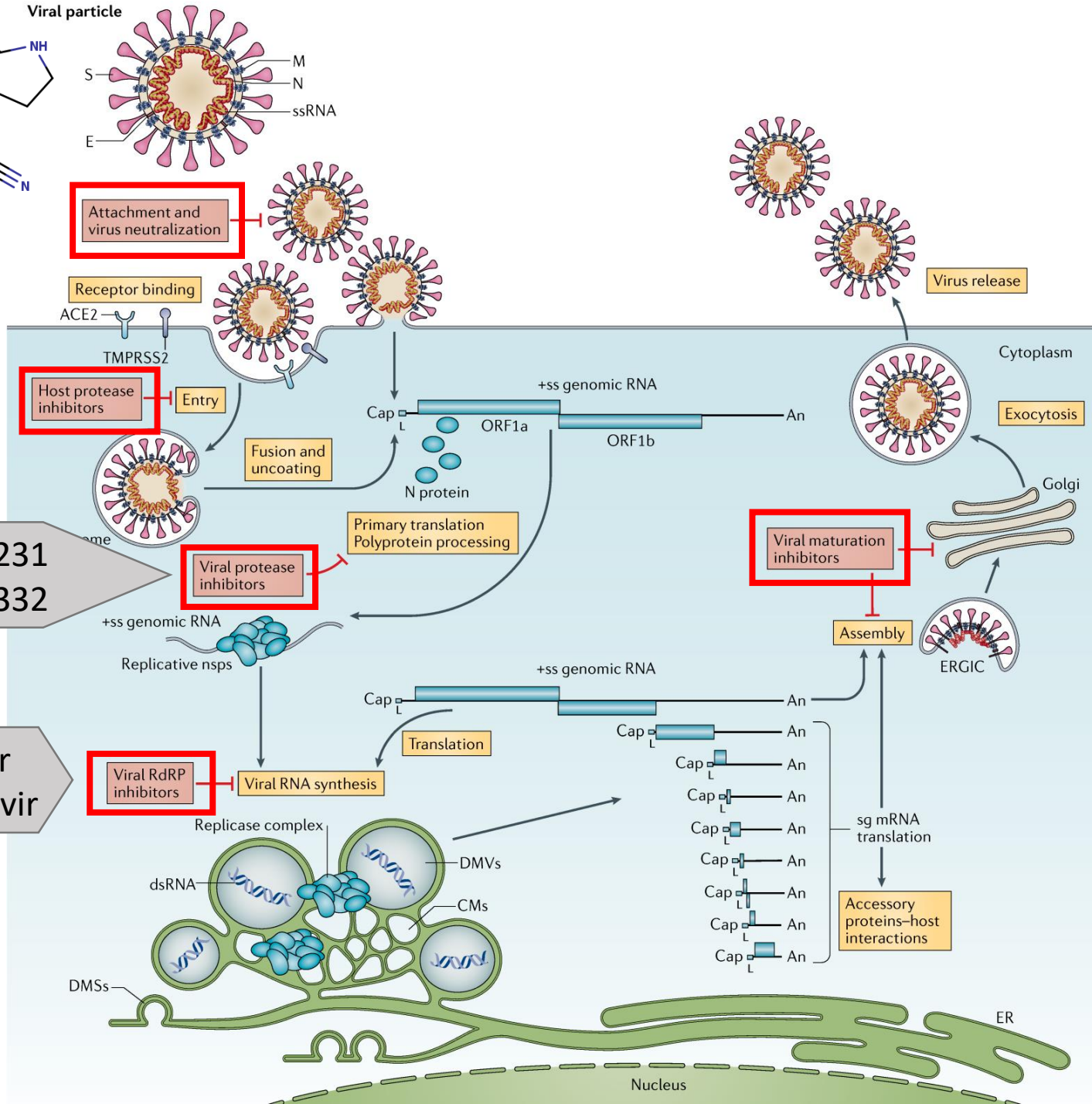
Remdesivir
Molnupiravir



Philip V'kovski et al. 2021. *Nature Reviews Microbiology.*

The goal of the study is to find a way to improve known perspective inhibitors of M^{pro} by computer methods.

To reach the goal we have achieved the next objectives:

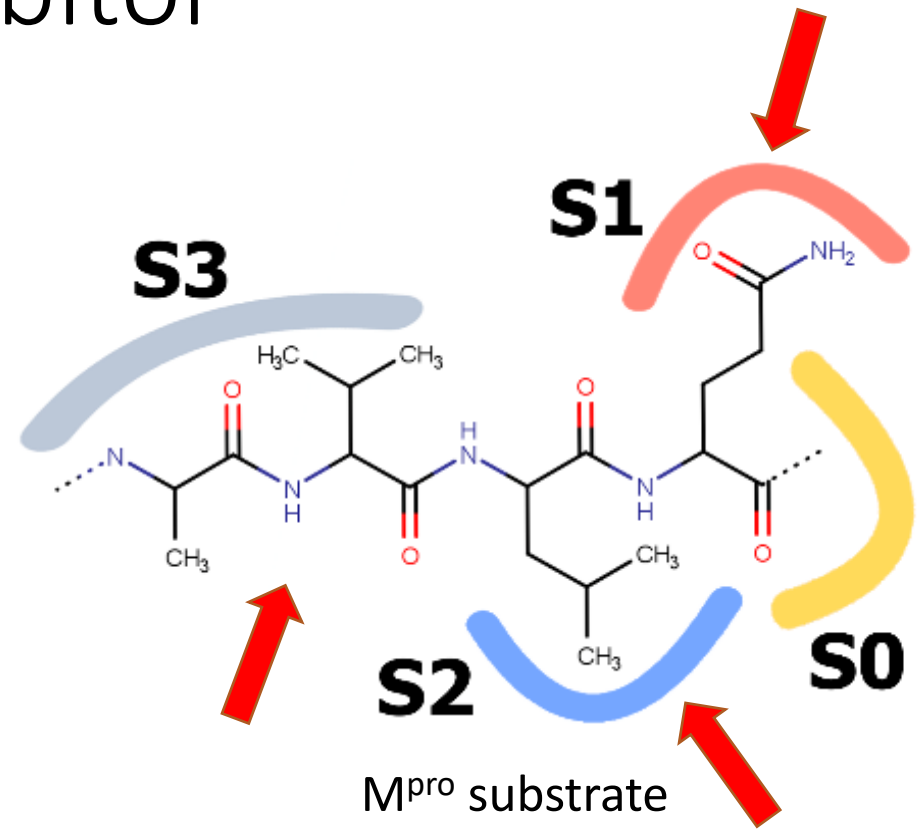
- to conduct an extensive review of Mpro inhibitors and understand structure-activity correlations;

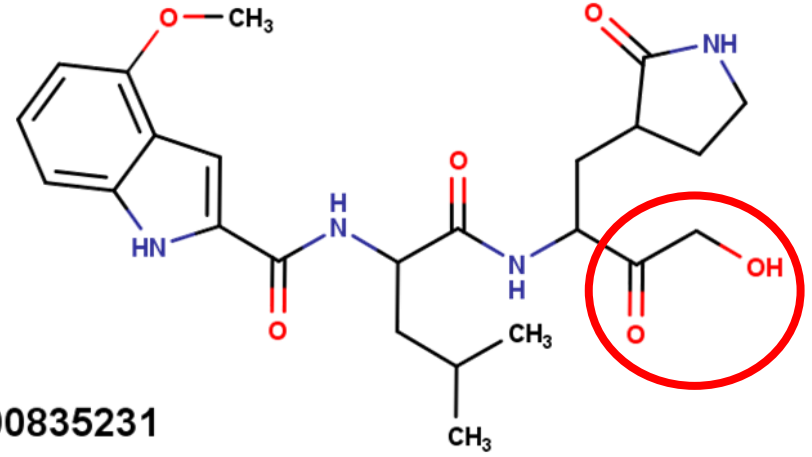
- assessment of pharmacokinetic parameters of known and about 50 new compounds using SwissADME online tool (Daina A. et al., 2017), the most attention was paid to solubility and GI absorption, because they define bioavailability;

- molecular dynamics simulations and binding energy calculations of about 20 selected compounds using GROMACS software (Abraham M.J. et al., 2015; Kumari R. et al., 2014).

Features of a good M^{pro} inhibitor

- S1 residue should resemble glutamine with one H-bond donor and one H-bond acceptor;
- S2 residue should have 3-bond length;
- a backbone need to be rigid for rapid binding and bulky somewhere at the left half (S3) for selectivity.





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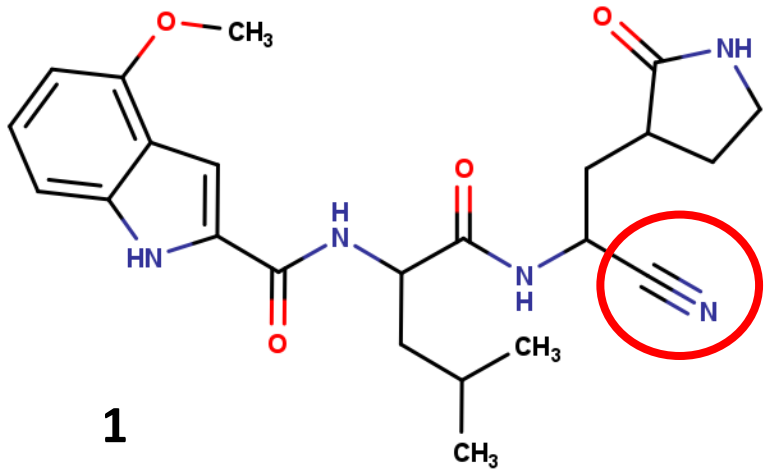

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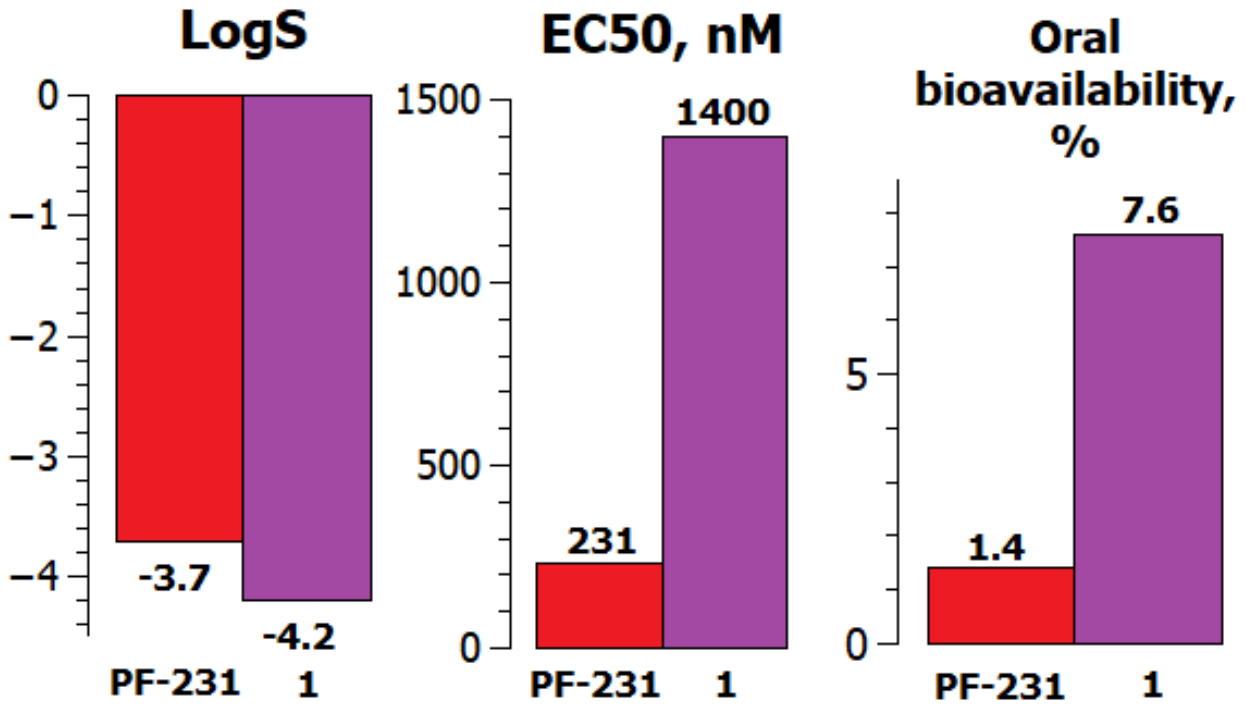

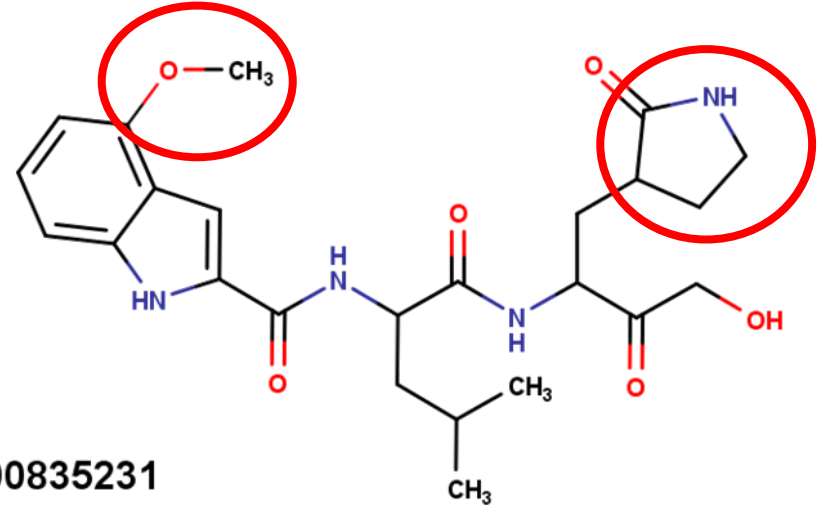

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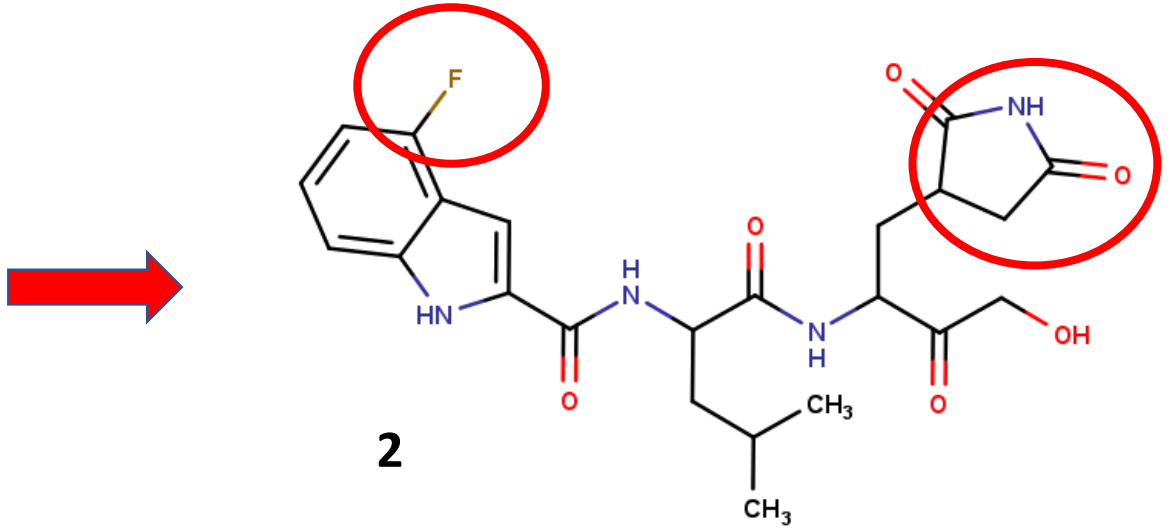

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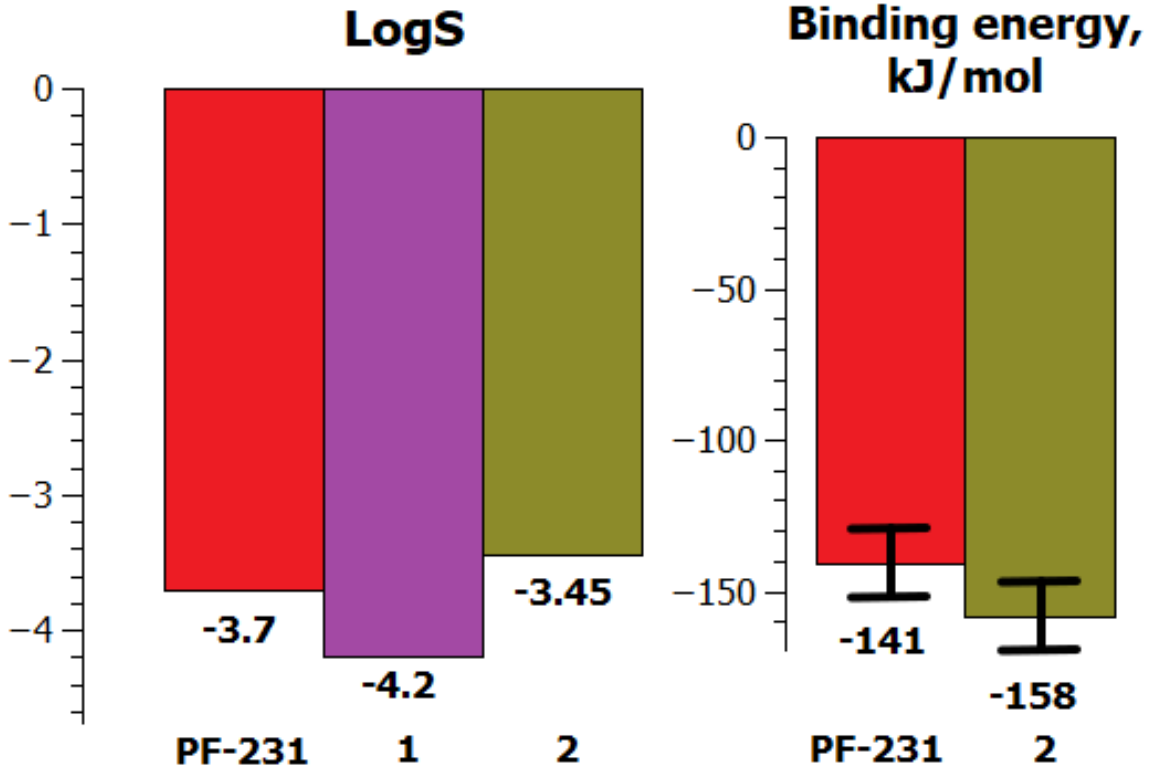

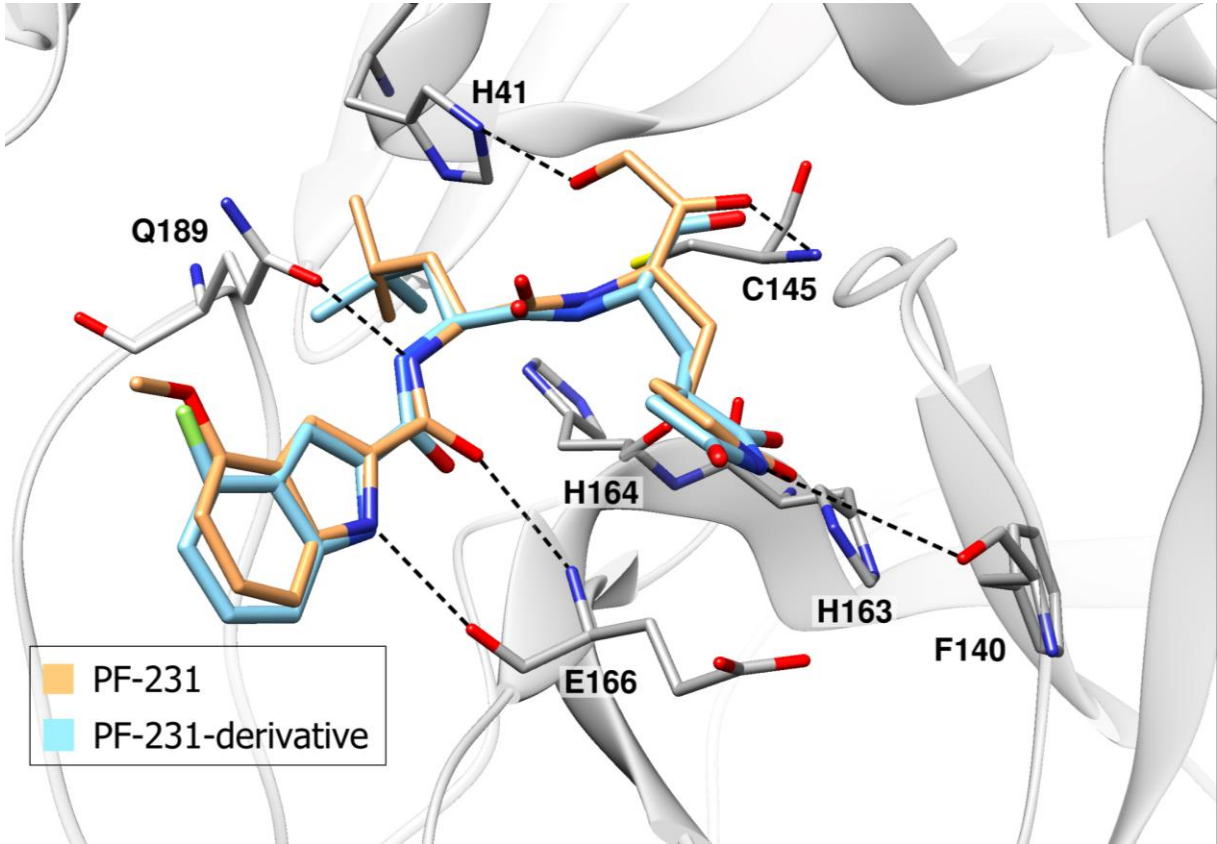

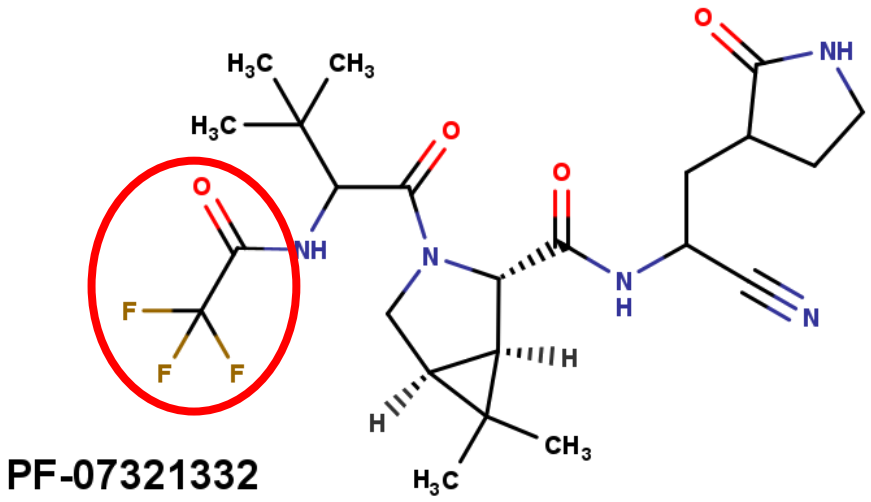
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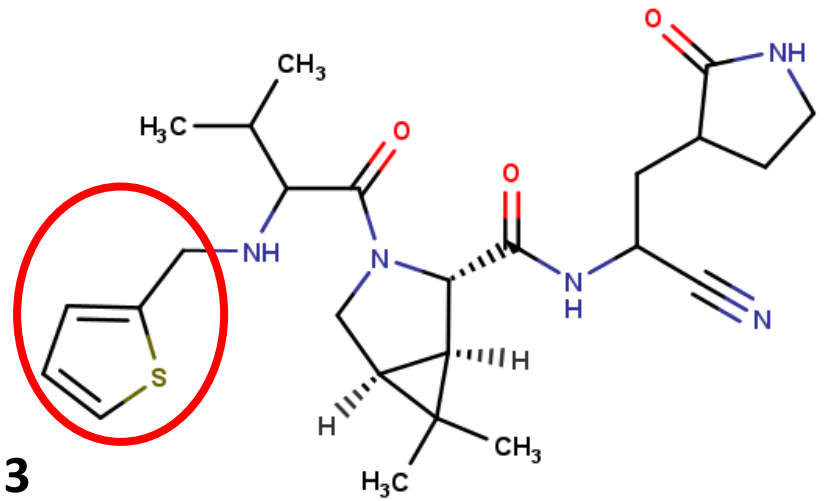
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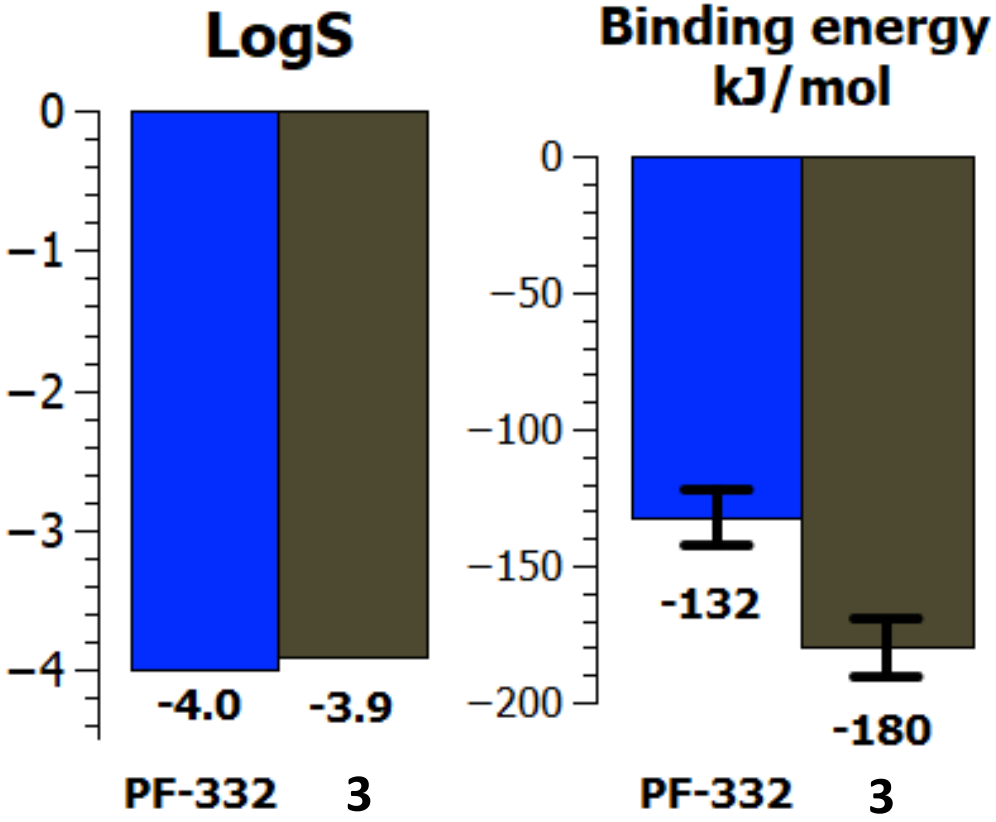
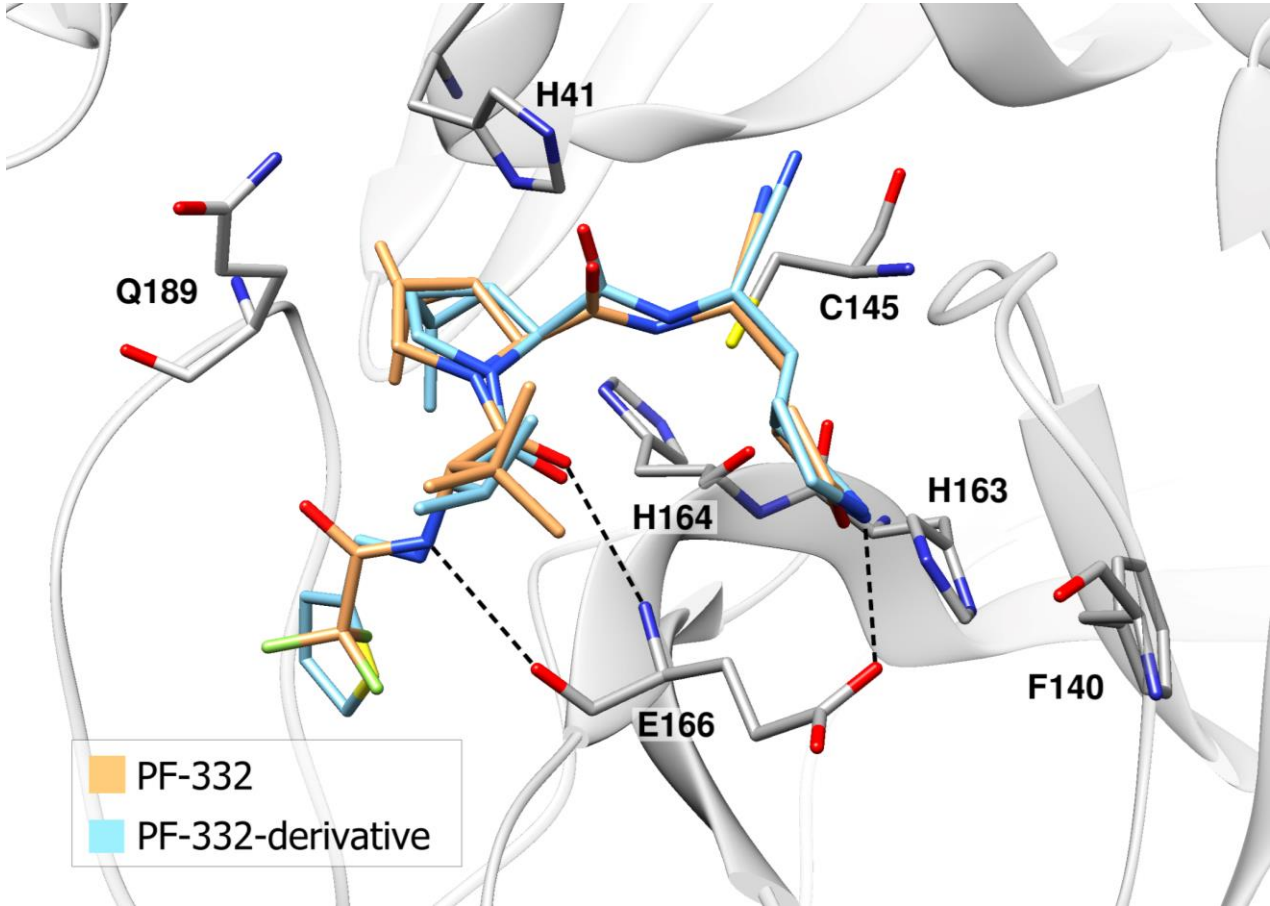

LogS
0
−1
−2
−3
−4
-4.0
-3.9
PF-332
3
Binding energy
kJ/mol
0
−50
−100
−150
−200
-132
-180
PF-332
3


H41
Q189
C145
H164
H163
E166
F140
PF-332
PF-332-derivative

frontiers in Pharmacology

Pre-Steady-State Kinetics of the SARS-CoV-2 Main Protease as a Powerful Tool for Antiviral Drug Discovery

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The design of effective target-specific drugs for COVID-19 treatment has become an intriguing challenge for modern science. The SARS-CoV-2 main protease, M^{pro}, responsible for the processing of SARS-CoV-2 polyproteins and production of individual components of viral replication machinery, is an attractive candidate target for drug discovery. Specific M^{pro} inhibitors have turned out to be promising anticoronaviral agents. Thus, an effective platform for quantitative screening of M^{pro}-targeting molecules is urgently needed. Here, we propose a pre–steady-state kinetic analysis of the interaction of M^{pro} with inhibitors as a basis for such a platform. We examined the kinetic mechanism of peptide substrate binding and cleavage by wild-type M^{pro} and by its catalytically inactive mutant C145A. The enzyme induces conformational changes of the peptide during the reaction. The inhibition of M^{pro} by boceprevir, telaprevir, GC-376, PF-00835231, or thimerosal was investigated. Detailed pre–steady-state kinetics of the interaction of the wild-type enzyme with the most potent inhibitor, PF-00835231, revealed a two-step binding mechanism, followed by covalent complex formation. The C145A M^{pro} mutant interacts with PF-00835231 approximately 100-fold less effectively. Nevertheless, the binding constant of PF-00835231 toward C145A M^{pro} is still good enough to inhibit the enzyme. Therefore, our results suggest that even noncovalent inhibitor binding due to a fine conformational fit into the active site is sufficient for efficient inhibition. A structure-based virtual screening and a subsequent detailed assessment of inhibition efficacy allowed us to select two compounds as promising noncovalent inhibitor leads of SARS-CoV-2 M^{pro}.

Thank you for your attention

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