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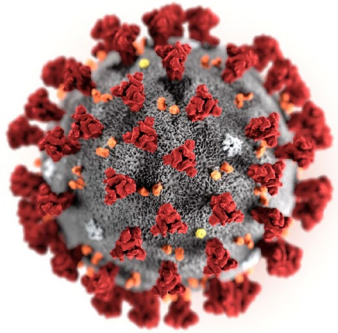

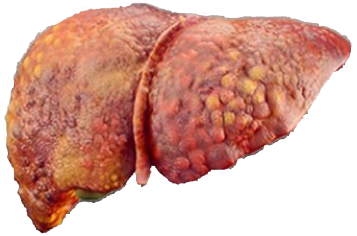

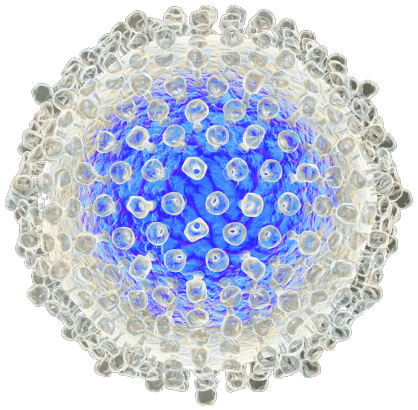

Dual Inhibition of SARS-CoV-2 and Human Rhinovirus with Protease Inhibitors in Clinical Development

Jerome Deval, March 24th, 2022

Disclosures

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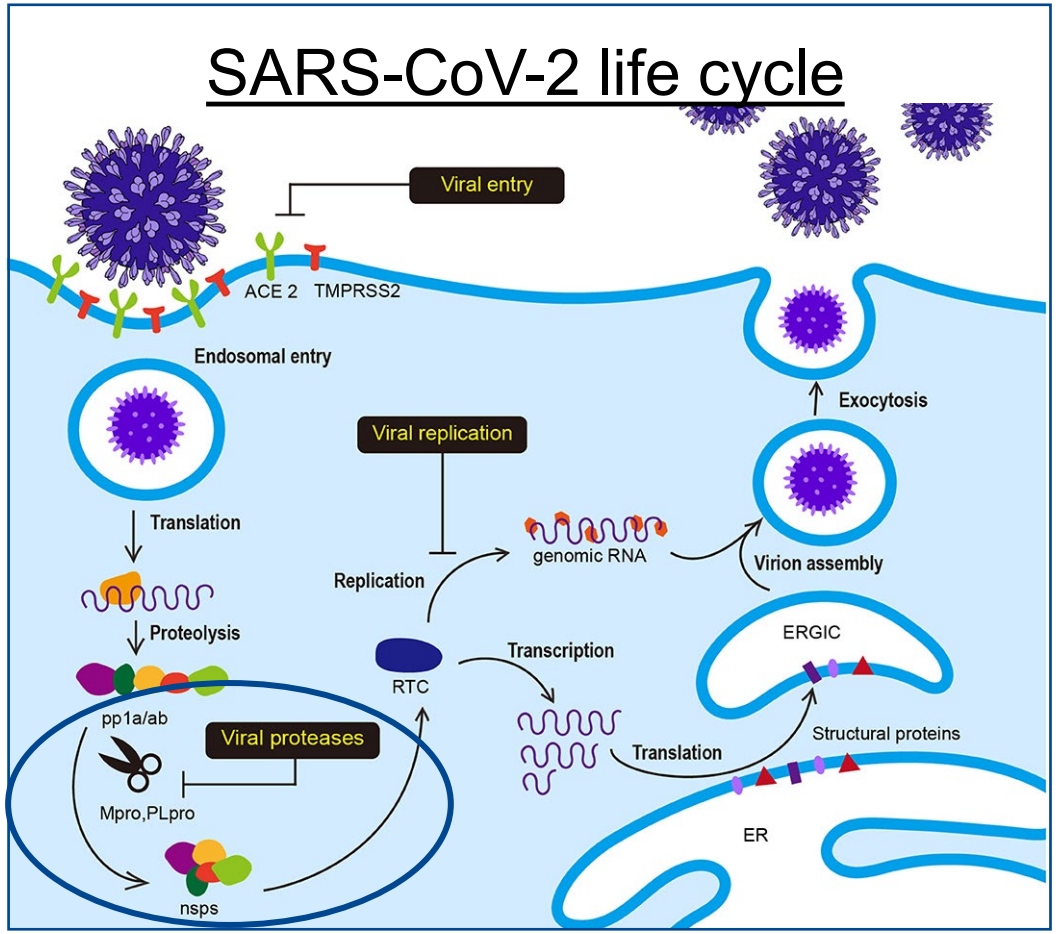
Except where otherwise indicated, the information contained in this presentation speaks as of the date hereof or as of the date at which such information is expressed to be stated, as applicable, and such information may express preliminary estimated, unaudited results which shall be subject to audit or other year-end adjustments and such audited or adjusted results may materially differ from those contained in this presentation.

This presentation concerns drug candidates, some of which are undergoing nonclinical studies and others of which are under clinical investigation, and all of which have not yet been approved for marketing by the U.S. Food and Drug Administration. These drug candidates are currently limited by federal law to investigational use, and no representation is made as to their safety or effectiveness for the purposes for which they are being investigated.

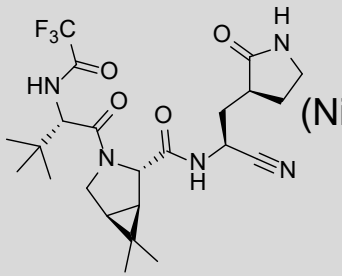
SARS-CoV-2 3CLpro Represents an Attractive Target

- Oral PIs are clinically validated (HIV/HCV)
- **Main protease (3CLpro) is conserved across CoVs and picornaviruses**
  - Pan-CoV coverage makes target attractive for possible future pandemics
- Emerging SARS-CoV-2 variants (alpha, beta, gamma, delta, lambda, omicron)
  - Are likely susceptible to 3CLpro inhibitors due to very few relevant mutations/polymorphism
- No human homolog of 3CLpro



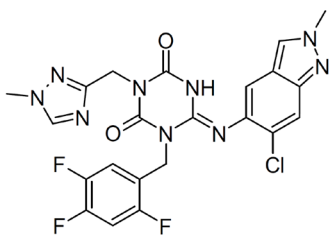
Oral SARS-CoV-2 3CLpro Inhibitors in Development

Approved in the US and Europe



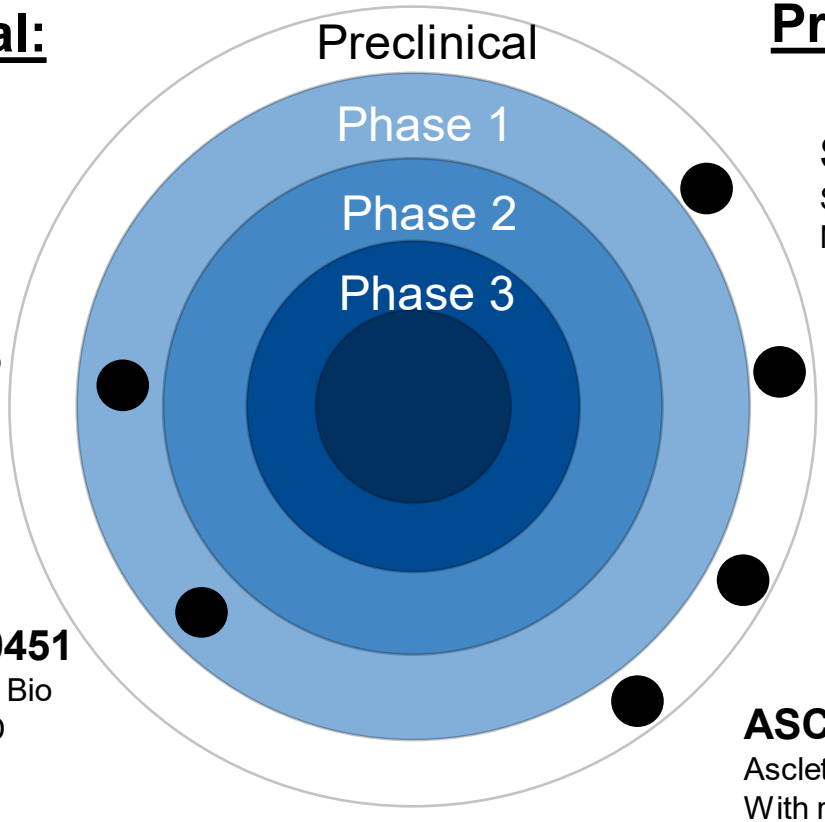
Nirmatrelvir
Pfizer
(Nirma. / PF-07321332)
PAXLOVID™
(Nirma. + ritonavir)
Oral BID dosing

Filed for approval in Japan



Ensitrelvir
Shionogi
Xocova™
(S-217622)
Oral QD dosing

Clinical:



EDP-235
Enanta
QD

PBI-0451
Pardes Bio
QD/BID

Preclinical:

STI-1558
Sorrento
No ritonavir

SH-879
Sosei Heptares
Grant funding from
Welcome trust

EDDC-2214
Everest medicines
Singapore EDDC

ASC-11
Ascletis
With ritonavir

Desired profile for a best-in-class : 1) QD/BID drug orally bioavailable without ritonavir
2) Broad pan-CoV spectrum, including resistance mutations and circulating variants

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Coronavirus PI Collaboration: CD3/Rega at KU Leuven

Centre for Drug Design and Discovery ("CD3")

CD3 | CENTRE FOR DRUG DESIGN AND DISCOVERY

Goal: to identify potent, selective coronavirus and rhinovirus PIs

Professor Johan Neyts
Rega Institute
KU Leuven

KU LEUVEN

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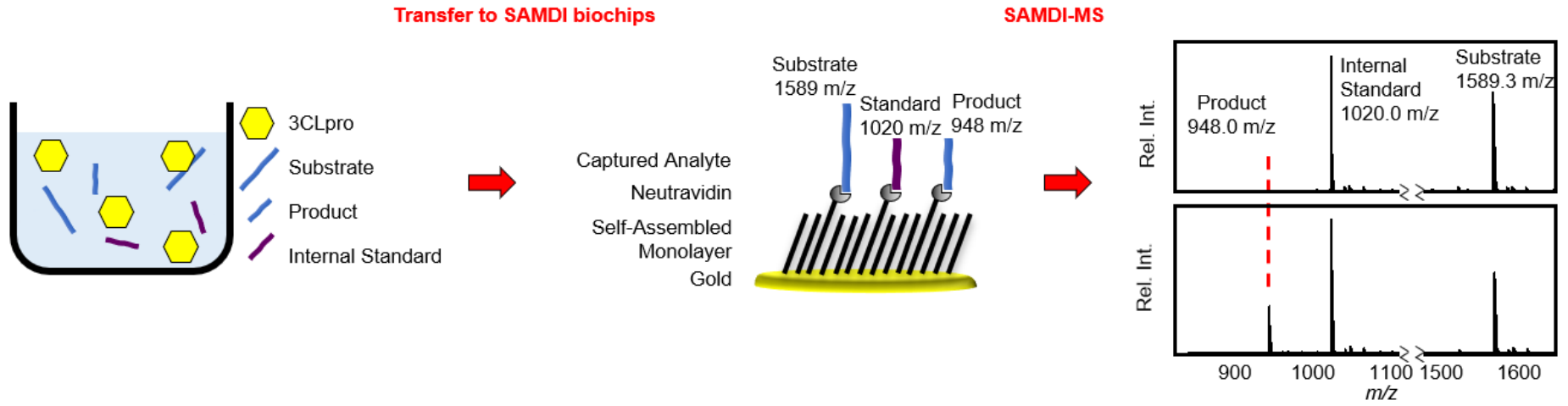
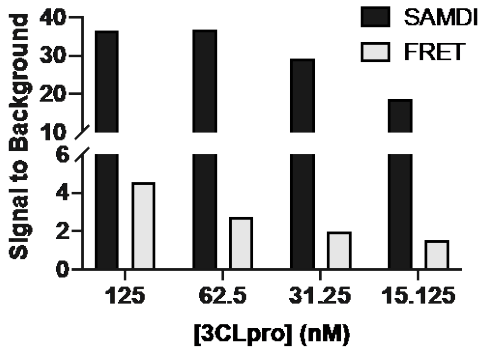
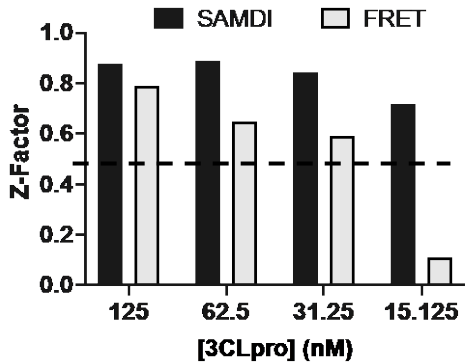
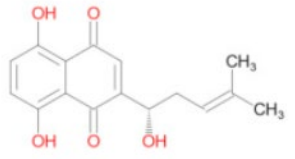
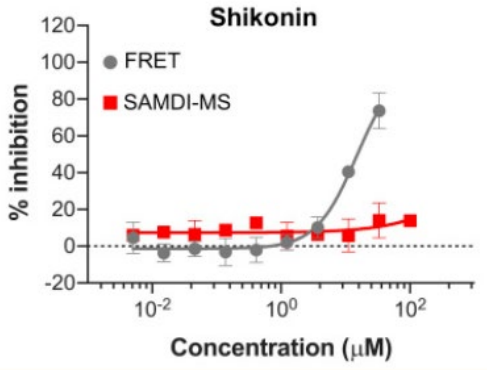
Comparison Between Standard FRET and SAMDI-MS Assay











Advantages of MS assay: 1) higher sensitivity, 2) lower propensity for false positive, and 3) can be multiplexed

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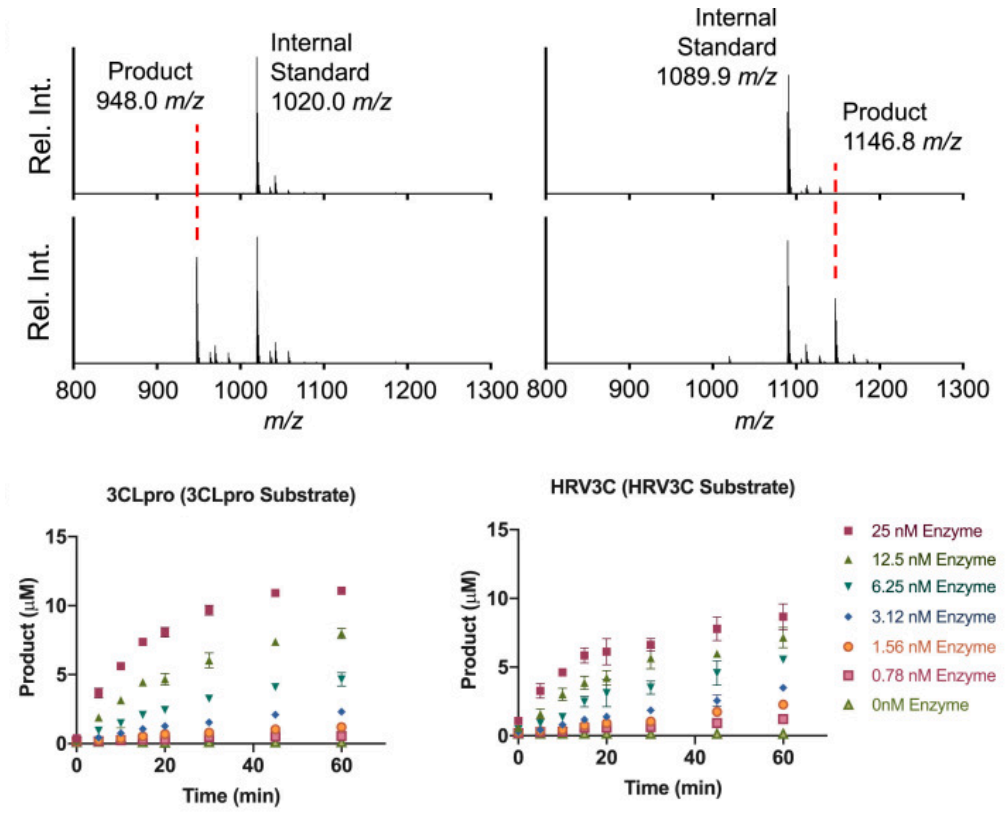
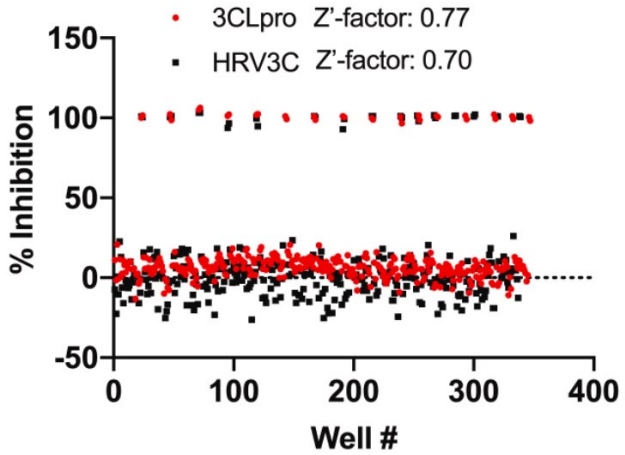
Antiviral Res. 2020 Oct;182:104924. doi: 10.1016/j.antiviral.2020.104924.

Next Step: Multiplex the Assay at Low Enzyme Concentration



- Monitoring the activity of SARS-CoV-2 3CLpro and human rhinovirus (HRV) 3C simultaneously
- Standard assay condition: 3 nM 3CLpro and 6 nM HRV3C (384-well plate)



Advantage: dual readout on SARS-CoV-2 and human rhinovirus proteases for all tested compounds

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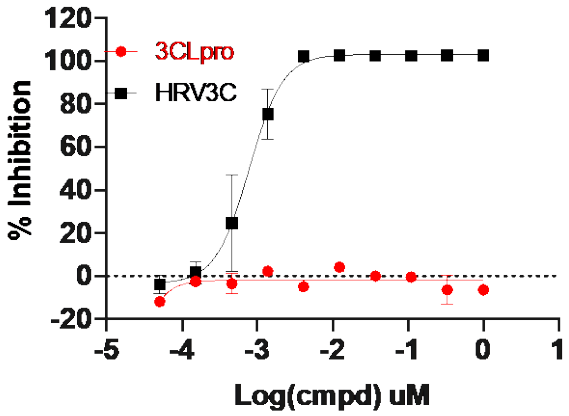
Biochem Biophys Res Commun. 2021 May 28;555:134-139.
Antiviral Res. 2021 Mar;187:105020. doi: 10.1016/j.antiviral.2021.105020.

Compound Selectivity Profile

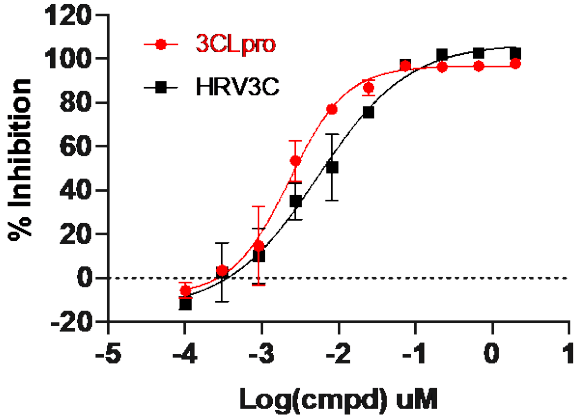
Rupintrivir



SELECTIVE (rhinovirus)

cathepsin L -

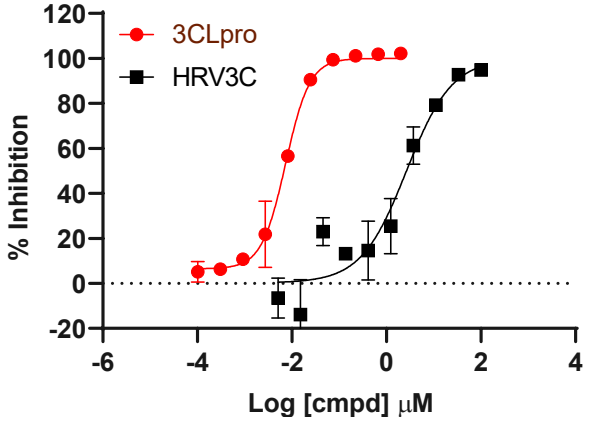
GC376



NON-SELECTIVE

cathepsin L +

PF-00835231



SELECTIVE (SARS-CoV-2)

Weak cathepsin L inhibitor

GC376 is non-selective: it inhibits both viral proteases as well as human cathepsin L

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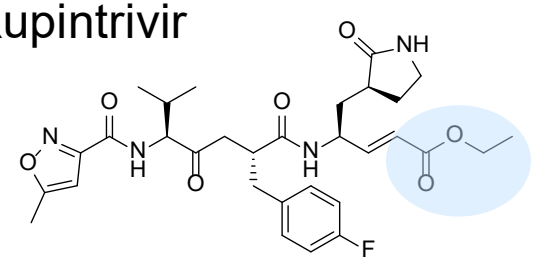
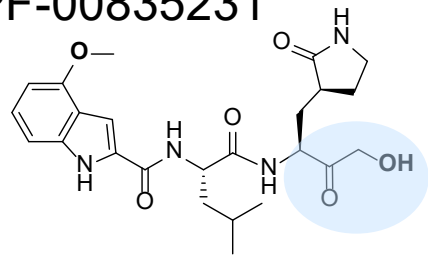
Antiviral Res. 2021 Mar;187:105020. doi: 10.1016/j.antiviral.2021.105020.

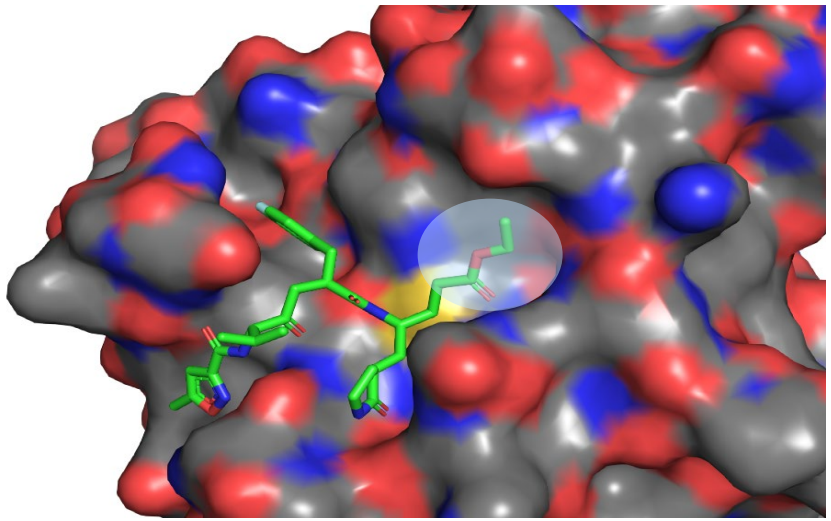
Optimization for Protease Selectivity

Rupintrivir

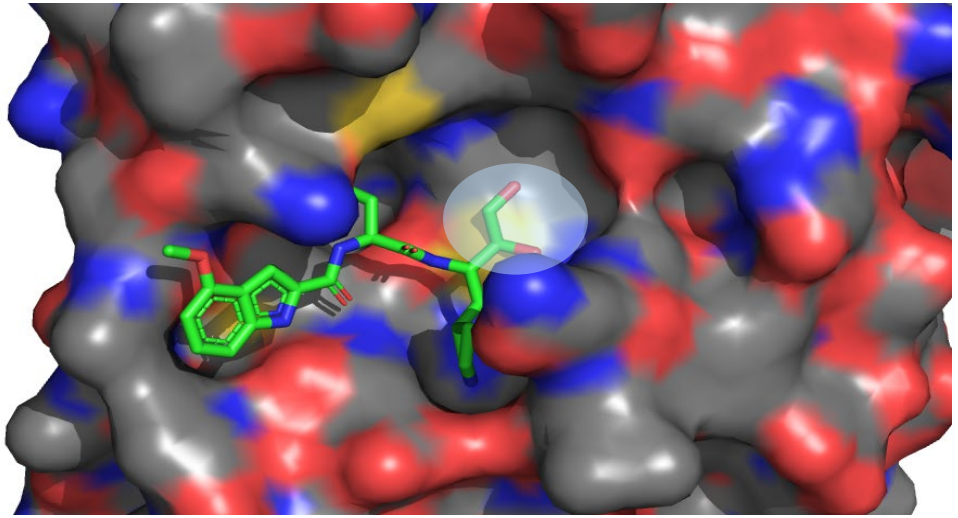


PF-00835231





HRV3C protease (PDB 1CQQ)



SARS-CoV-2 3CLpro (PDB 6XMH)

Compounds were optimized to maximize ligand occupancy beyond covalent binding of warhead to cysteines

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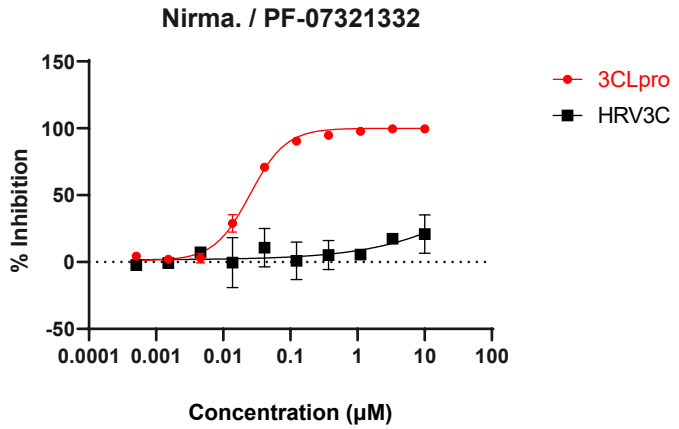
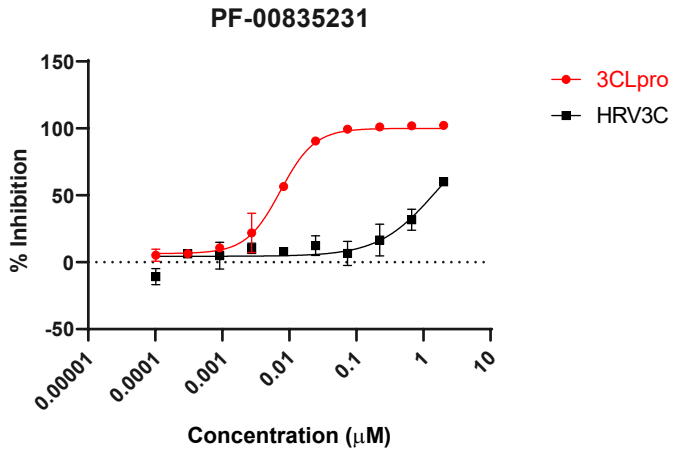
Antiviral Res. 2021 Mar;187:105020. doi: 10.1016/j.antiviral.2021.105020.

Enzyme Titration with Tight Binding Inhibitors





	SARS-CoV-2 3CLpro IC_{50} (nM)	SARS-CoV-2 3CLpro Hillslope	HRV 3C Protease IC_{50} (nM)	Cathepsin L IC_{50} (nM)
Nirma.	17.9 ± 6.6	1.25*	> 10000	> 10000
PF-00835231	5.48 ± 1.78	1.70*	1675 ± 1000	172 ± 134

* High hillslope (>1) is indicative of enzyme titration.

At 3 nM 3CLpro: risk of under-predicting compound potency with tight binding inhibitors

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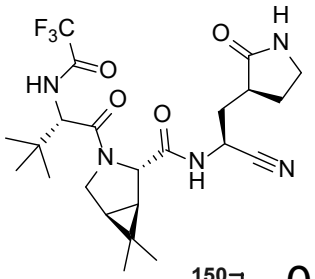
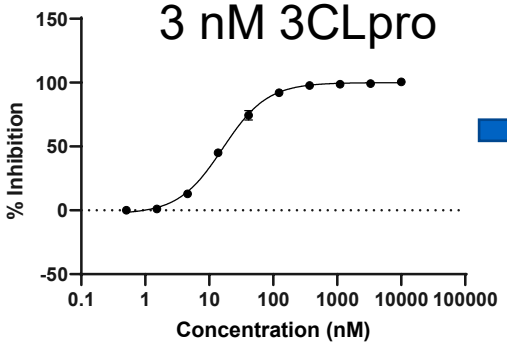
Further Reducing Enzyme Concentration

- Lower 3CLpro enzyme (from 3 to 0.3 nM) provides a more sensitive assay that was developed to address the issue of enzyme titration with very potent compounds (IC_{50} < 10 nM)

Nirmatrelvir
(Nirma. / PF-07321332)

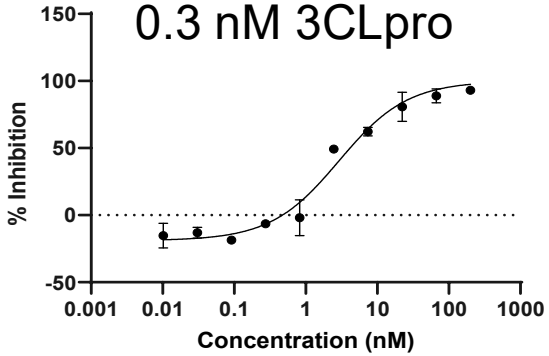


3 nM 3CLpro

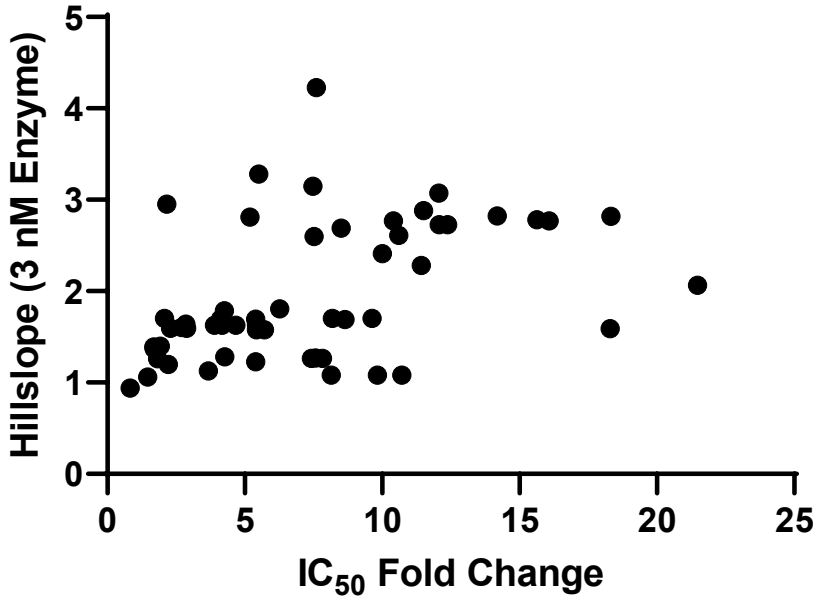


IC_{50} (nM) = 18 nM
Hillslope = 1.25

0.3 nM 3CLpro



IC_{50} (nM) = 2.9 nM, K_i = 2.03 nM
Hillslope = 0.91



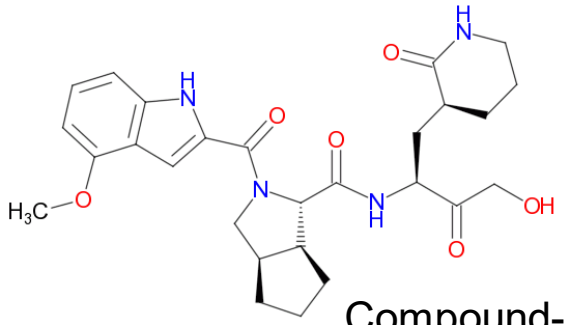
Using low protease concentration is needed to accurately assess the potency of tight binding inhibitors

A Few Words About Resistance to 3CLpro Inhibitors

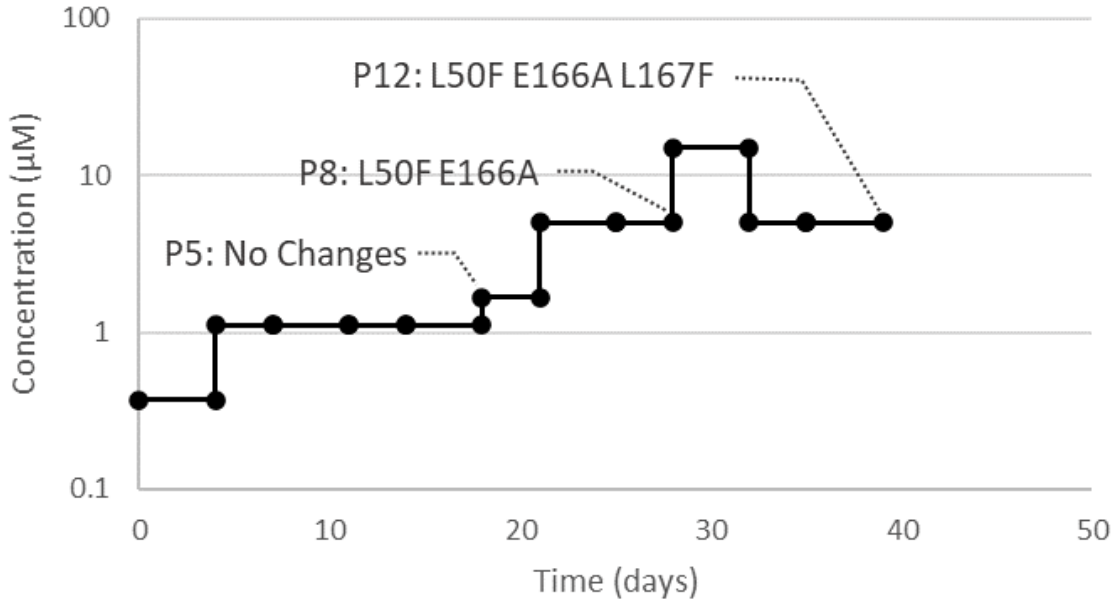
KU LEUVEN

- Resistance selection performed at Rega/KU Leuven with Compound-1 (Early Lead)
- Passaging of SARS-CoV-2 in VeroE6 cells in the presence of increasing concentrations of Compound-1 resulted in the selection of mutations at amino acids 50, 166 and 167

More details shown in poster
Liu C. et al., Abstract 214



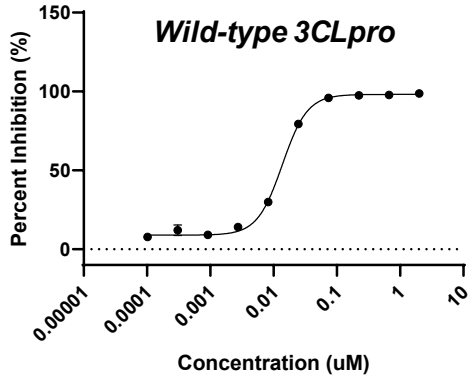
Compound-1

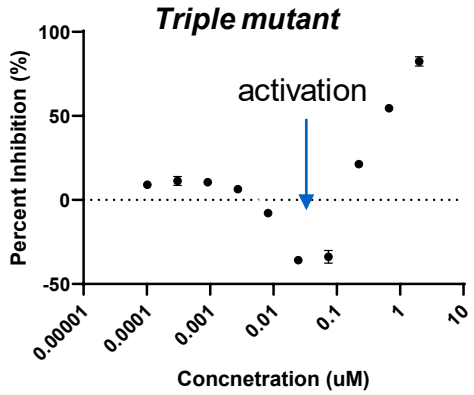


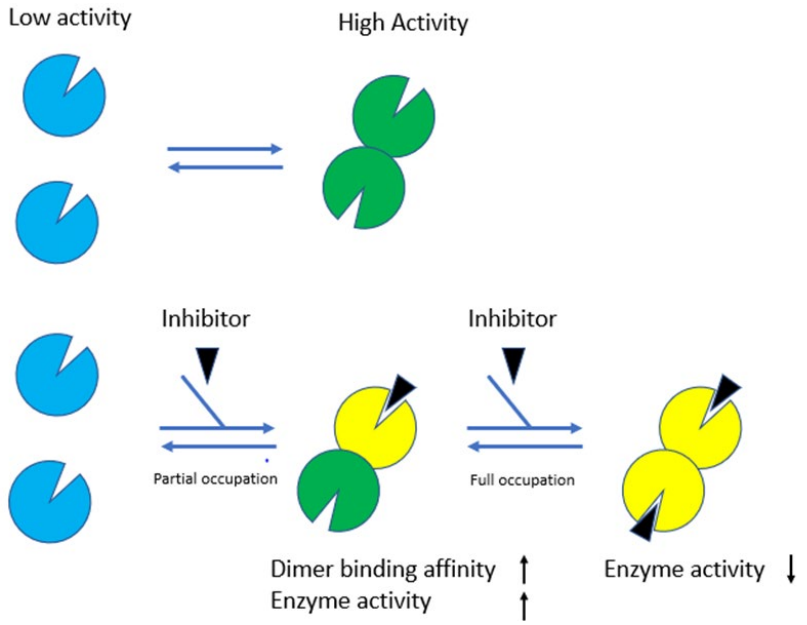
Passaging of SARS-CoV-2 with compound-1 resulted in selection of 3 amino acid mutations

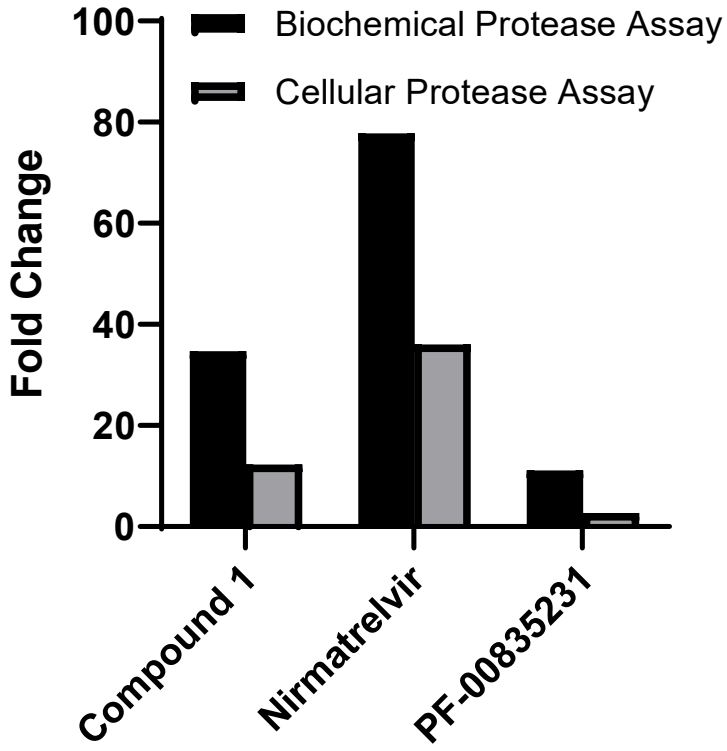
Effect of Mutations on Resistance to 3CLpro Inhibitors

Compound #1









The triple mutant conferred resistance to compound-1 and nirmatrelvir, but not to '231

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Liu C. et al., ICAR 2022 Abstract 214

Summary and Conclusion

- The need to develop improved 2nd generation inhibitors of 3CLpro remains high
- Robust and sensitive biochemical assays are key to differentiate inhibitors during drug discovery
- Here, we described a novel biochemical assay with dual readout for SARS-CoV-2 and rhinovirus proteases
  - Validated with known selective inhibitors of each enzyme
  - More sensitive and less prone to false positives than the FRET format
- Picomolar concentration of 3CLpro was required to avoid enzyme titration and underprediction of tight binding inhibitor potency

Our next goal: to understand the activity profile of 3CLpro inhibitors against all major resistance mutations and circulating variants

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Thank you!

Rega Institute KU Leuven

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