Univerza v Mariboru

Laboratory of Physical Chemistry and Chemical Thermodynamics

National Supercomputing Forum (NSCF-2022)

Application of HPC resources on SARS-CoV-2 research

plenary lecture

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Coronaviruses are our everyday companions

Beta-coronavirus (50-200 nm in diameter)

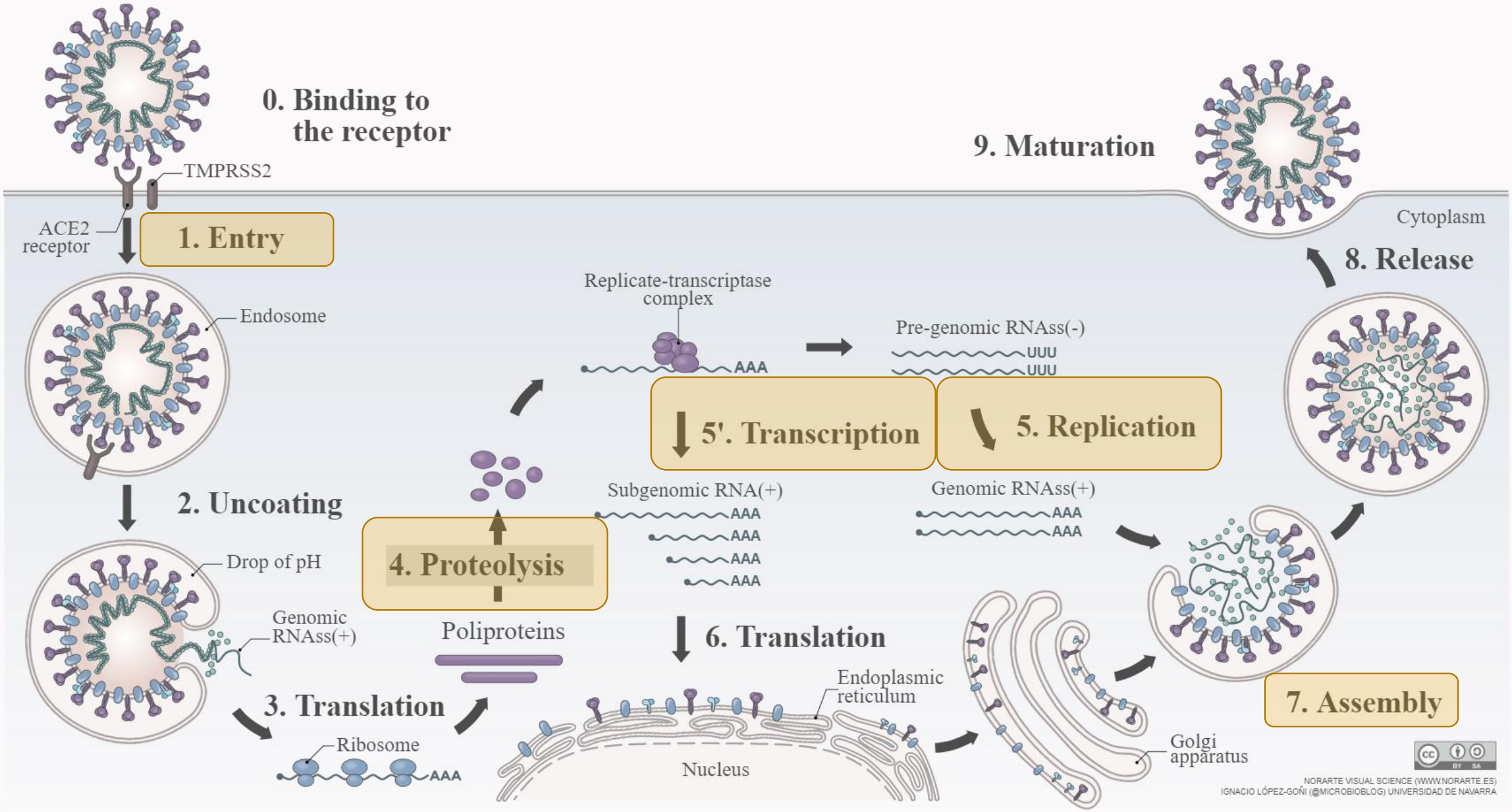
- Coronaviruses are named after crown spikes located on their surface.
- Four major subgroups of coronaviruses: α, β, γ and δ
- Human coronaviruses were discovered in the mid-1960s.
- Common human coronaviruses from the *Coronavirinae* subfamily in the *Coronaviridae* family, which often causing common colds are: 229E (alpha coronavirus); NL63 (alpha coronavirus); OC43 (beta coronavirus); HKU1 (beta coronavirus) .
- Sometimes coronaviruses, which usually infect animals, can skip to human hosts. Such viruses are especially dangerous because humans do not yet have the protective mechanisms in place.

Pandemic...

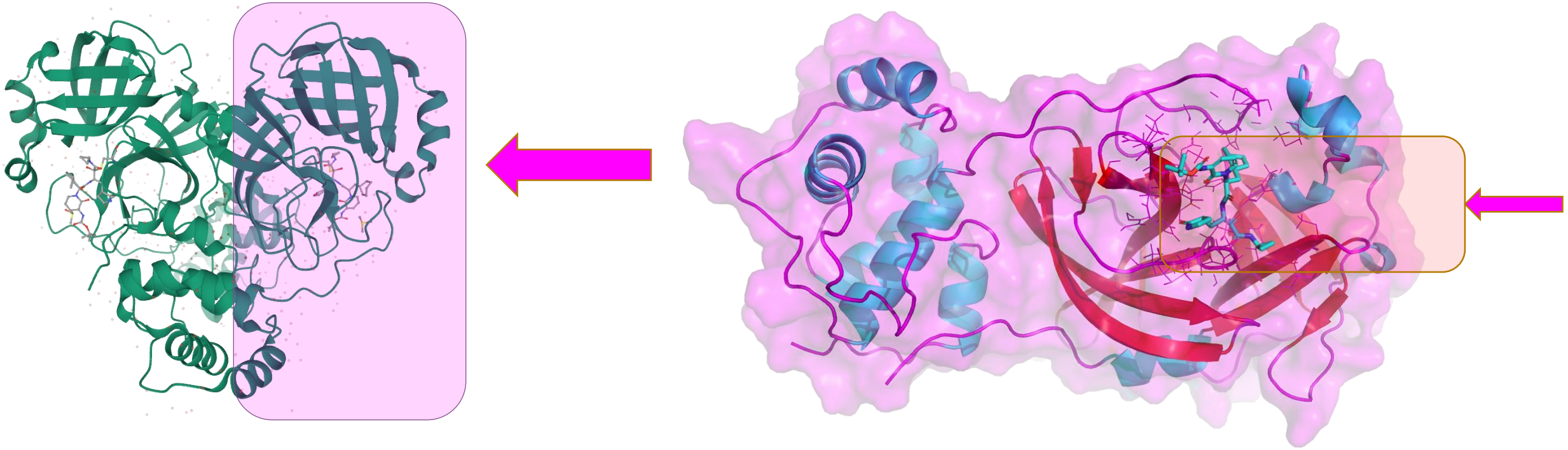
Previous occurrences of related pathogens can be traced to 2003 when coronaviruses were reported to cause severe acute (**SARS**) and Middle East (**MERS**) respiratory syndromes [1][2][3]. The novel virus (initially 2019-nCoV now named SARS-CoV-2; 'n' - novel) was reported in December of 2019 to be originating from Wuhan, Hubei China [4]. In the early **2020, the virus spread, causing a global pandemic** [5][6][7]. COVID-19 disease is of grave global concern because, while the majority of cases displays mild symptoms, a variable percentage (0.2 to > 5 %!) of patients progresses to pneumonia and multi-organ failure leading to potential death, especially without medical assistance [8][9].

[1] de Wit E, van Doremalen N, Falzarano D, Munster VJ. SARS and MERS: recent insights into emerging coronaviruses. Nat. Rev. Microbiol. 2016; 14:523-534.
[2] Hilgenfeld R, Peiris M. From SARS to MERS: 10 years of research on highly pathogenic human coronaviruses. Antivir Res. 2013; 100:286-295.
[3] Lu G, Wang Q, Gao GF. Bat-to-human: spike features determining 'host jump'of coronaviruses SARS-CoV, MERS-CoV, and beyond. Trends Microbiol. 2015; 23:468-478.
[4] Wu F, Zhao S, Yu B, Chen YM, Wang W, Song ZG, et al. A new coronavirus associated with human respiratory disease in China. Nature. 2020; 579:265-269.
[5] Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, Xing X, et al. Early transmission dynamics in Wuhan, China, of novel coronavirus–infected pneumonia. N Engl J Med. 2020; 382:1199-1207.
[6] Hui DS, I Azhar E, Madani TA, Ntoumi F, Kock R, Dar O, et al. The continuing 2019-nCoV epidemic threat of novel coronaviruses to global health—The latest 2019 novel coronavirus outbreak in Wuhan, China. Int J Infect Dis. 2020; 91:264-266.
[7] Wang C, Horby PW, Hayden FG, Gao GF. A novel coronavirus outbreak of global health concern. Lancet. 2020; 395: 470-473.
[8] Johns Hopkins; Mortality Analyses https://coronavirus.jhu.edu/data/mortality. Accessed 25.4.2021
[9] O'Driscoll M, Dos Santos GR, Wang L, Cummings DA, Azman AS, Paireau, J, Fontanet A, Cauchemez S, Salje, H. Age-specific mortality and immunity patterns of SARS-CoV-2. Nature 2021; 590: 140-145.

Viral Life Cycle

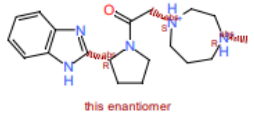
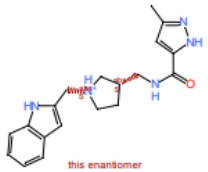
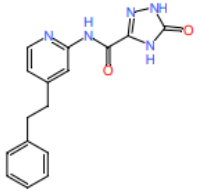
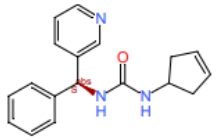
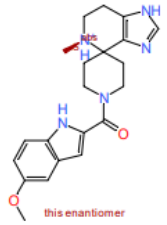


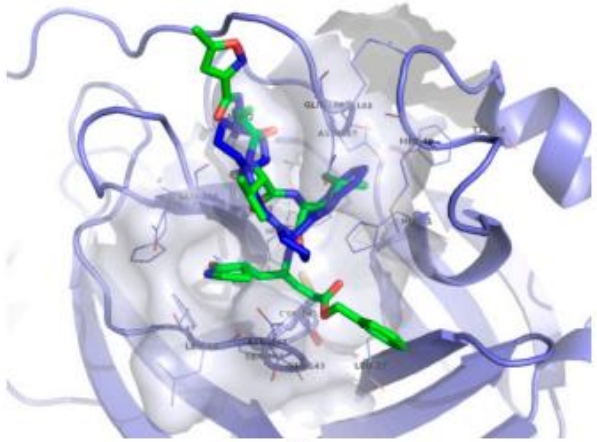
1. Development of viral main protease 3CL^{pro} inhibitors



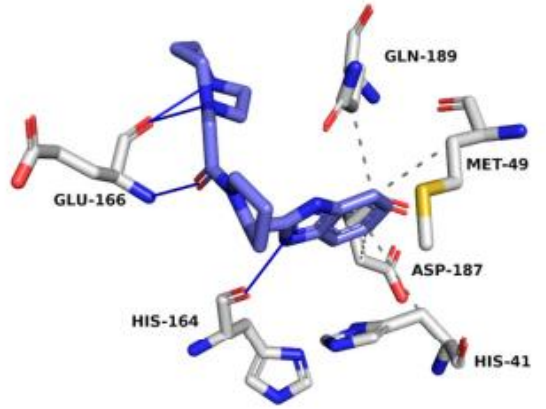
Processing of initial translated polyproteins into functional molecules. Currently the most researched protease is the **3C-like proteinase** (**3CL^{pro}**). It is a cysteine protease under clan PA, MEROPS classification C30.

1. Development of viral main protease 3CL^{pro} inhibitors

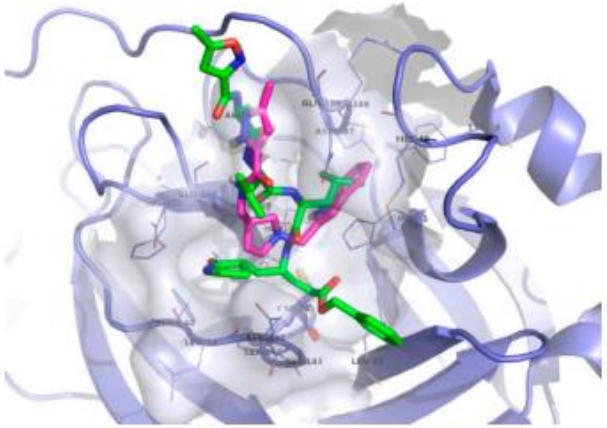
No.	Structure	Mr (g/mol)	Binding Mode	Fred Docking Score [1]
1	 this enantiomer	343.5	P2–P3	−14.5
2	 this enantiomer	338.4	P2–P3	−13.5
3		309.3	P2–P3	−13.0
4	 this enantiomer	293.4	P1′–P2	−13.0
5	 this enantiomer	380.5	P1′–P2	−13.0



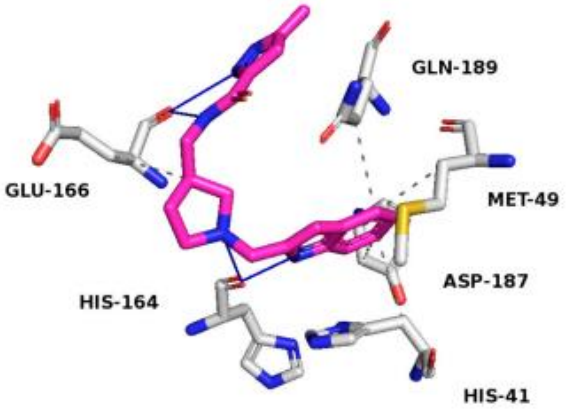
(a)



(b)



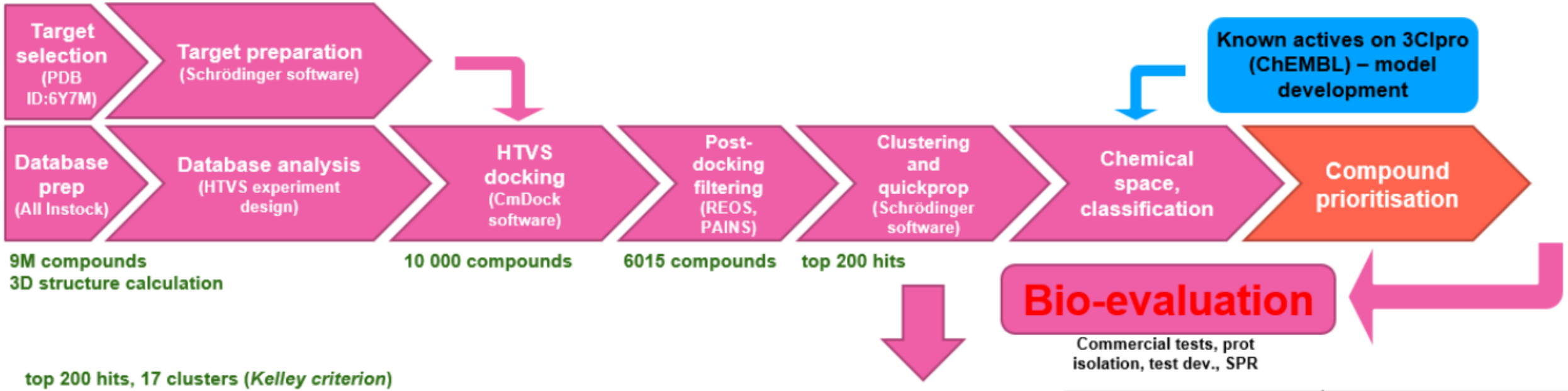
(c)



(d)

Compound	Free VdW (kcal/mol)	Free Coulomb (kcal/mol)	Complex VdW Weighted Sum (kcal/mol)	Complex Coulomb Weighted Sum (kcal/mol)	ΔG^{BIND}_{LIE} (kcal/mol)
1	−16.2 ± 0.2	−32.3 ± 0.1	−22.0 ± 1.4	−37.3 ± 2.4	−8.2 ± 1.9
2	−14.7 ± 0.2	−19.0 ± 0.1	−22.5 ± 2.4	−18.7 ± 2.6	−3.5 ± 1.7

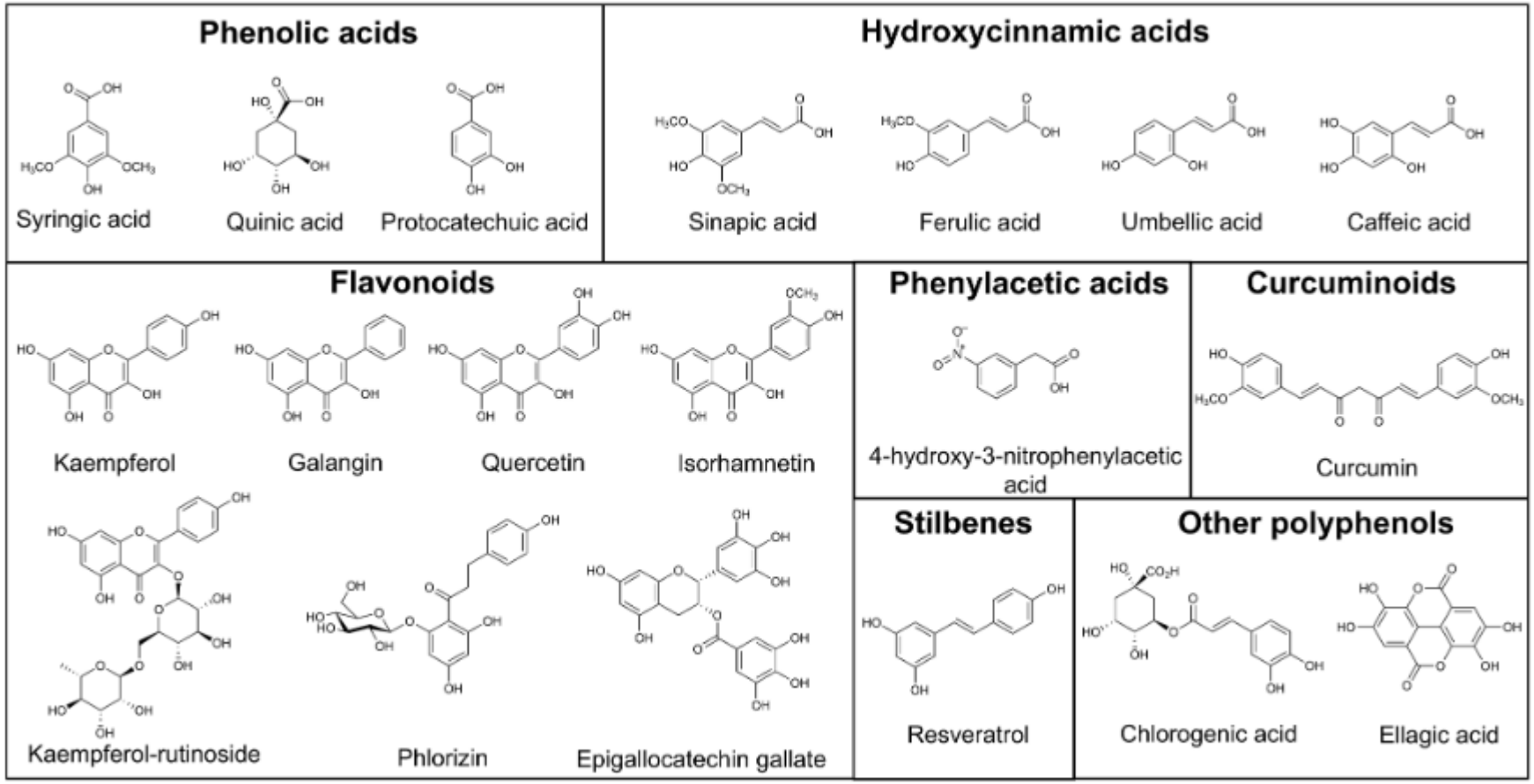
2. Further prioritization of compounds for 3CL^{pro} research



Testing of ML pipelines for compound classification and activity regression.

3. Natural compound elaboration for 3CL^{pro} research

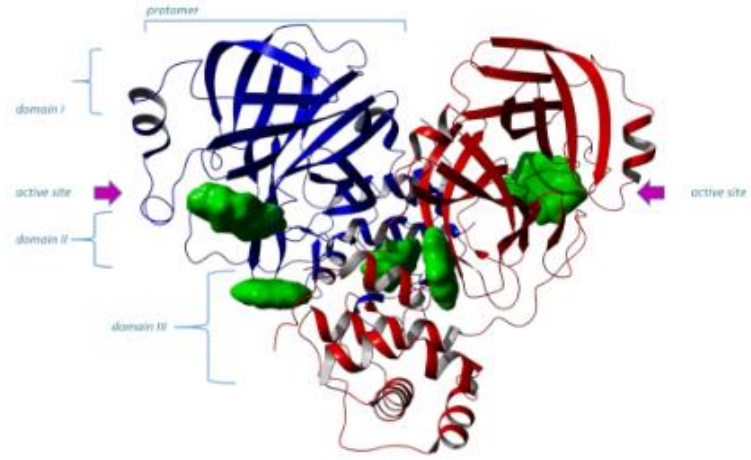
Inhibition of the SARS-CoV-2 3CL pro main protease by plant polyphenols



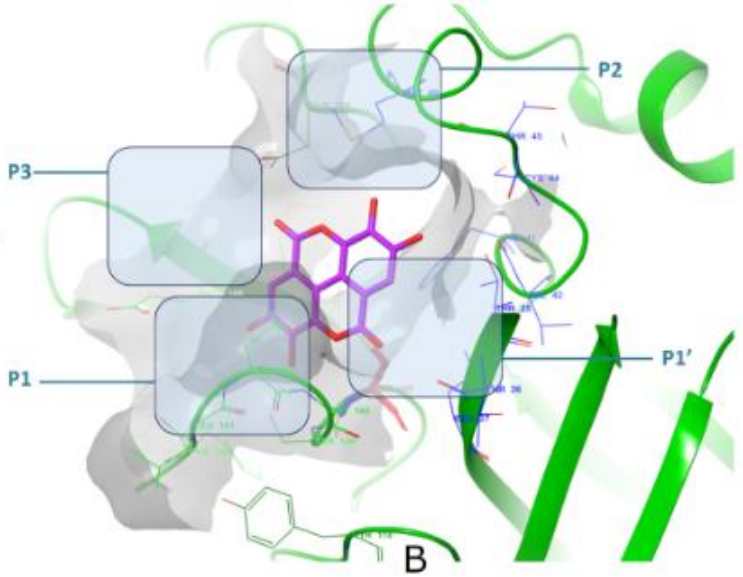
Potential for drug design?

3. Natural compound elaboration for 3CL^{pro} research

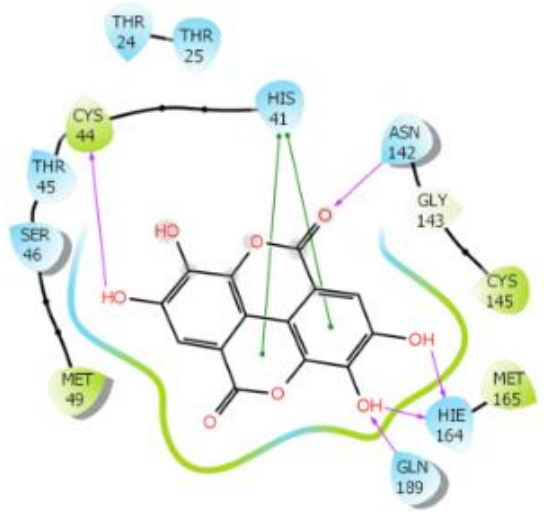
Inhibition of the SARS-CoV-2 3CL pro main protease by Ellagic acid.



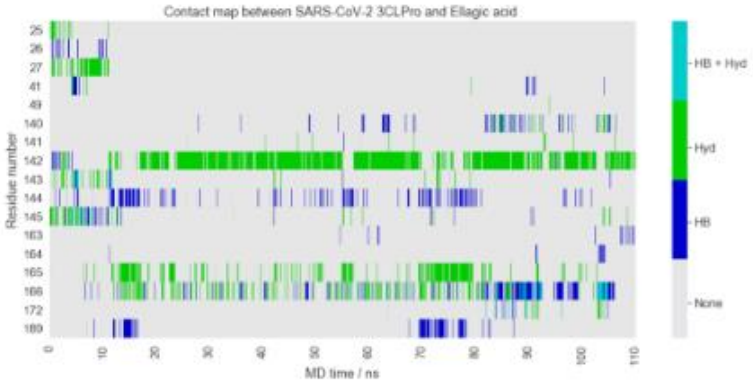
A



B



C

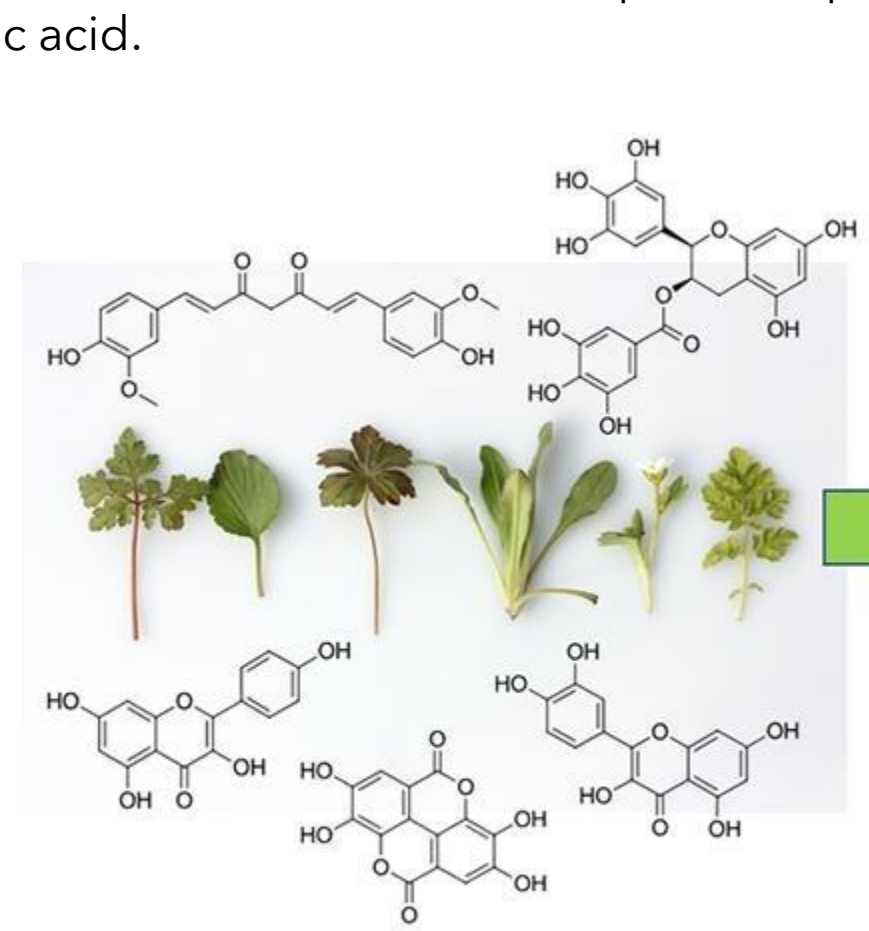


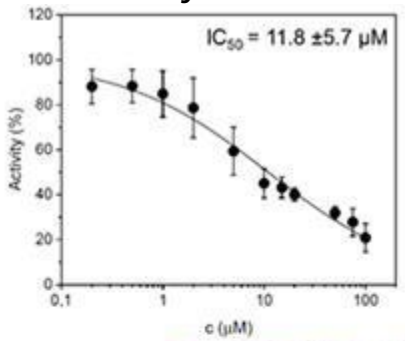
D

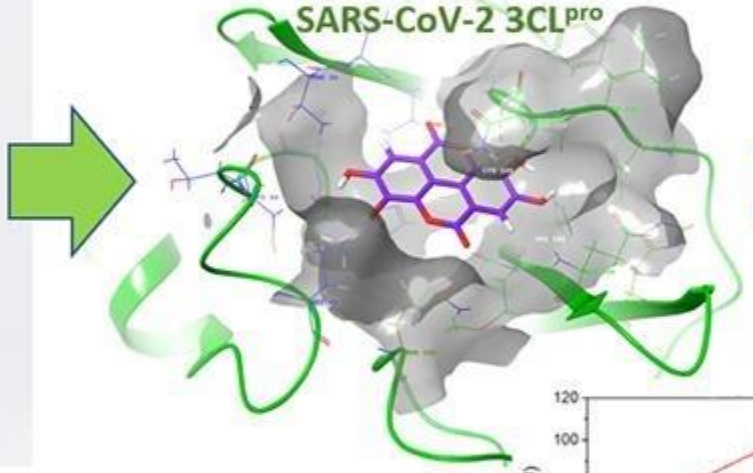
However...

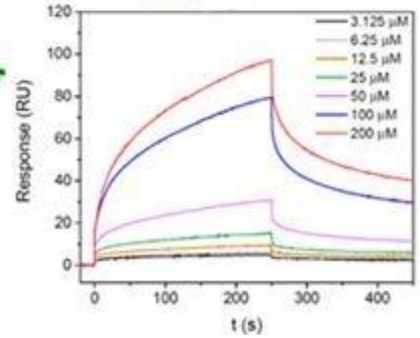
3. Natural compound elaboration for 3CL^{pro} research

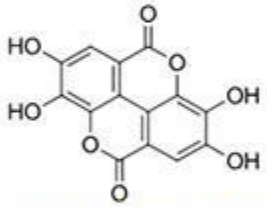
Inhibition of the SARS-CoV-2 3CL pro main protease by Ellagic acid.











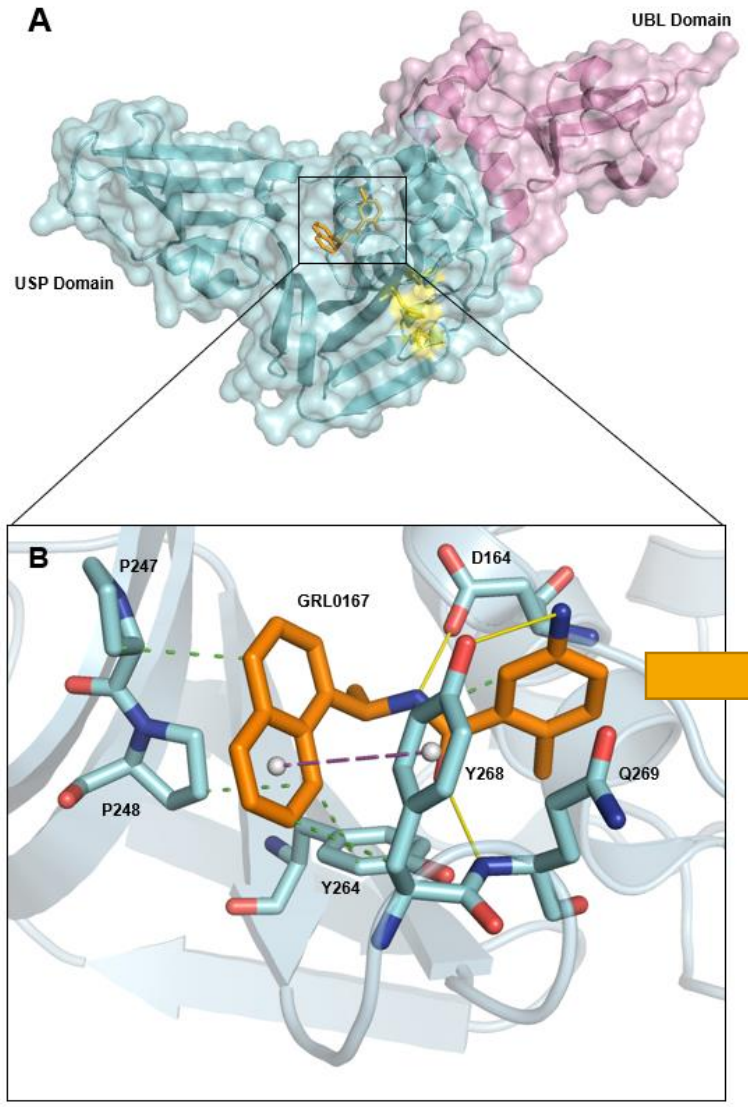
ELLAGIC ACID

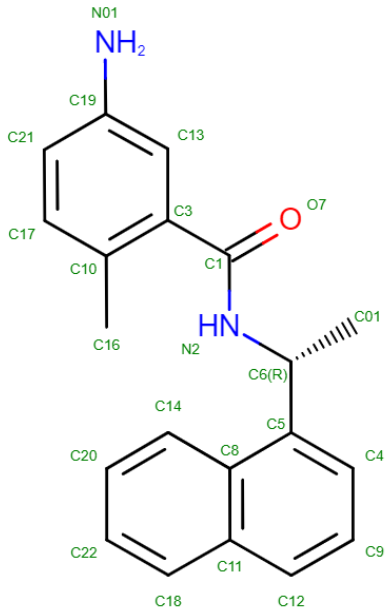
IC_{50} = 11.8 µM

K_D = 311 ± 69 µM

IC_{50}s low, good for scaffold hopping, future design!

4. Development of papain-like protease PL^{pro} inhibitors

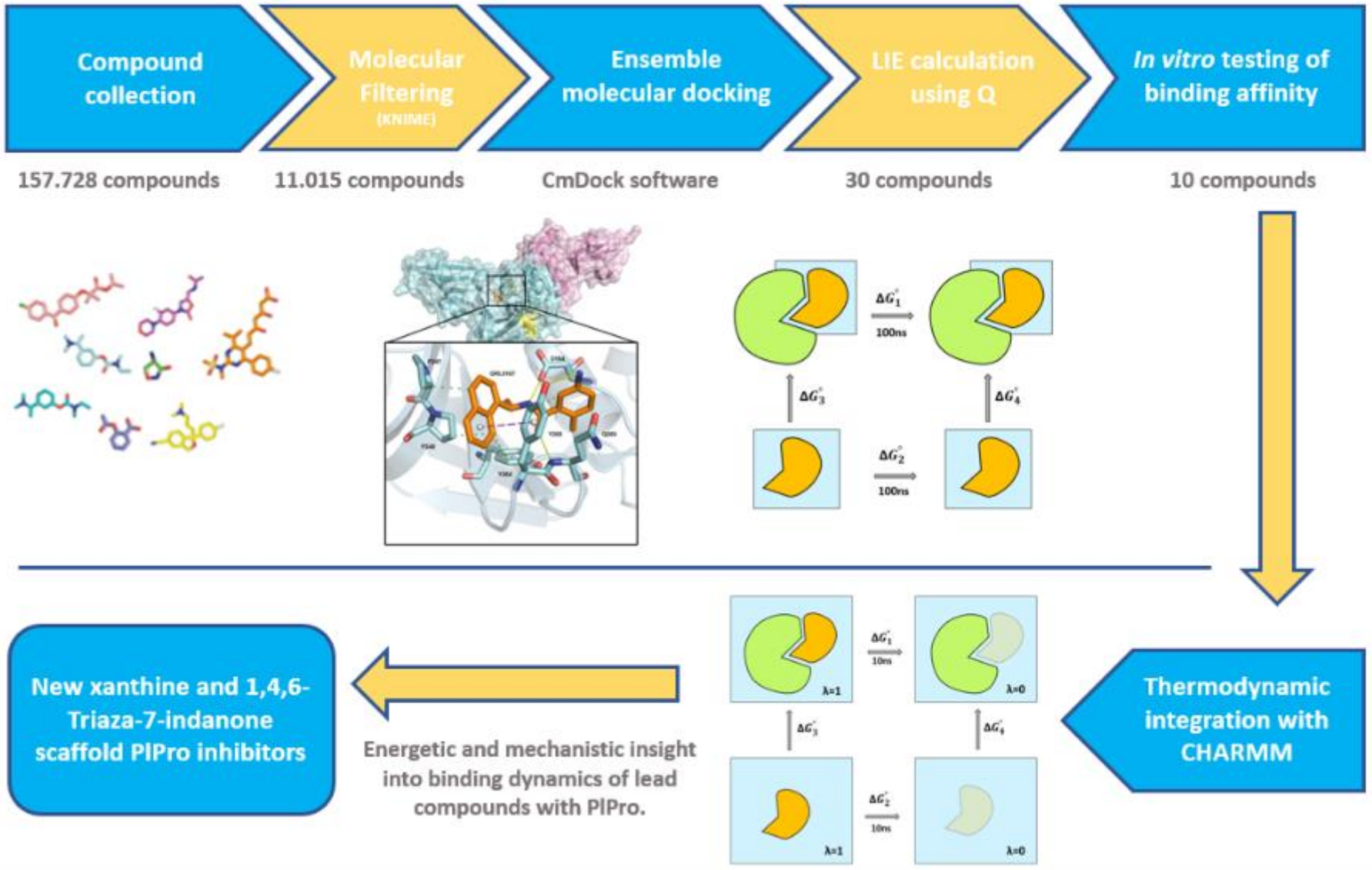




GRL0617
PDB ID:
7cmd

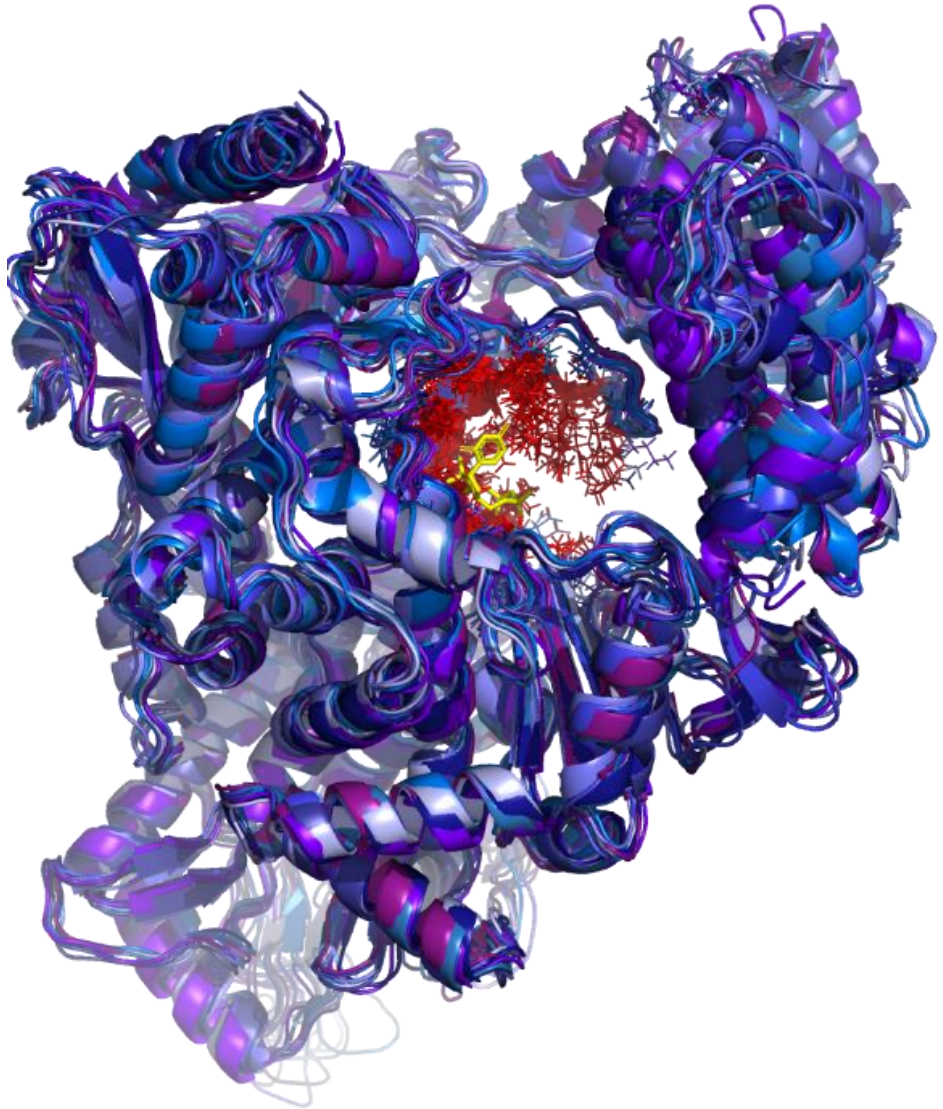
Also splits the viral poliprotein into several functioning proteins, allowing viral replication inside the cells.

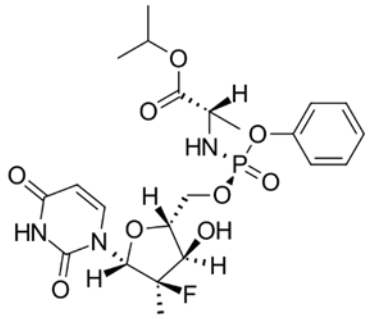
4. Development of papain-like protease PL^{pro} inhibitors



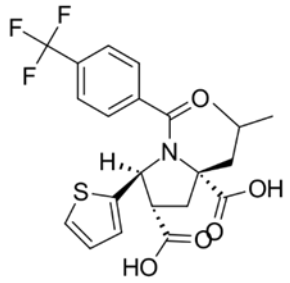
5. Development of SARS-CoV-2 RdRp inhibitors

Novel Thioether-Amide or Guanidine-Linker Class of SARS-CoV-2 Virus RNA-Dependent RNA Polymerase Inhibitors

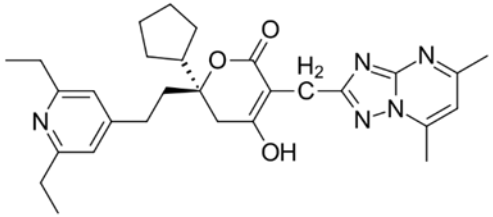




Sofosbuvir

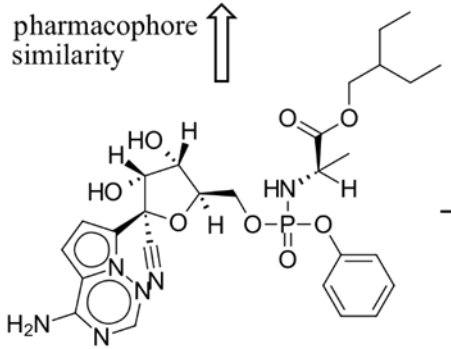


pubchem: 5275422



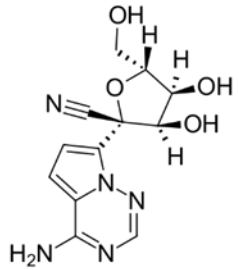
Filibuvir

pharmacophore similarity



Remdesivir (in development - SARS-CoV-2)

prodrug

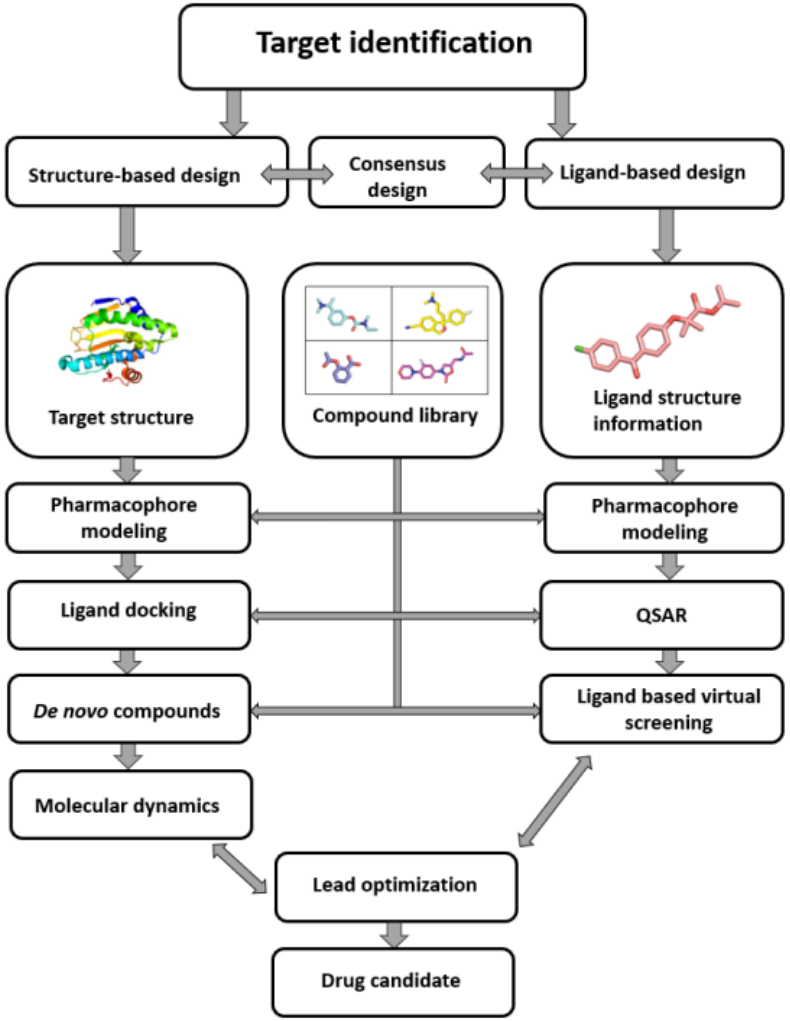


GS-441524

active form

6. Elaboration on libraries for SARS-CoV-2 inhibitor design

Are commercial libraries useful, can we do better for the community?



Application of chemical libraries

6. Elaboration on libraries for SARS-CoV-2 inhibitor design

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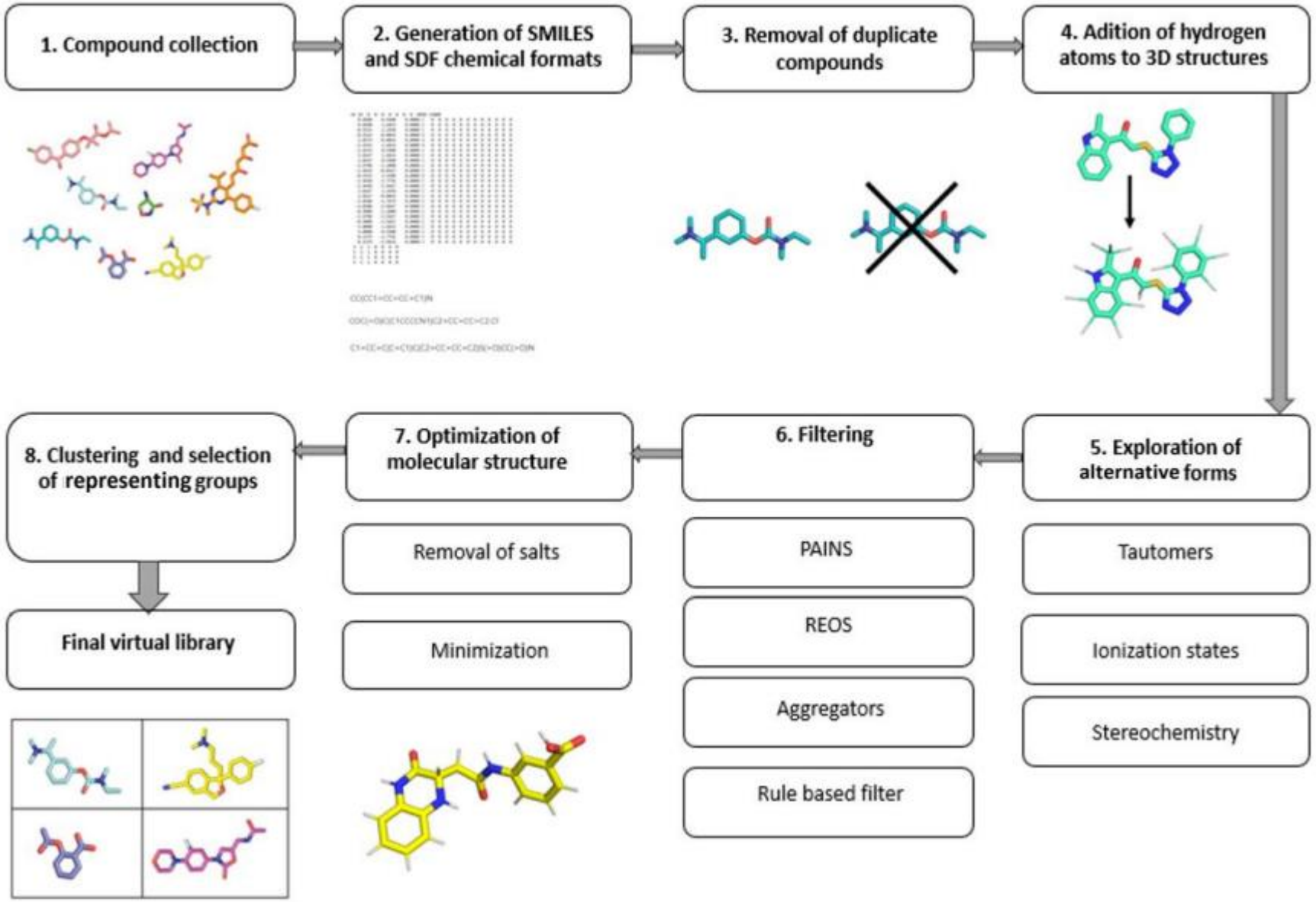

6. Elaboration on libraries for SARS-CoV-2 inhibitor design

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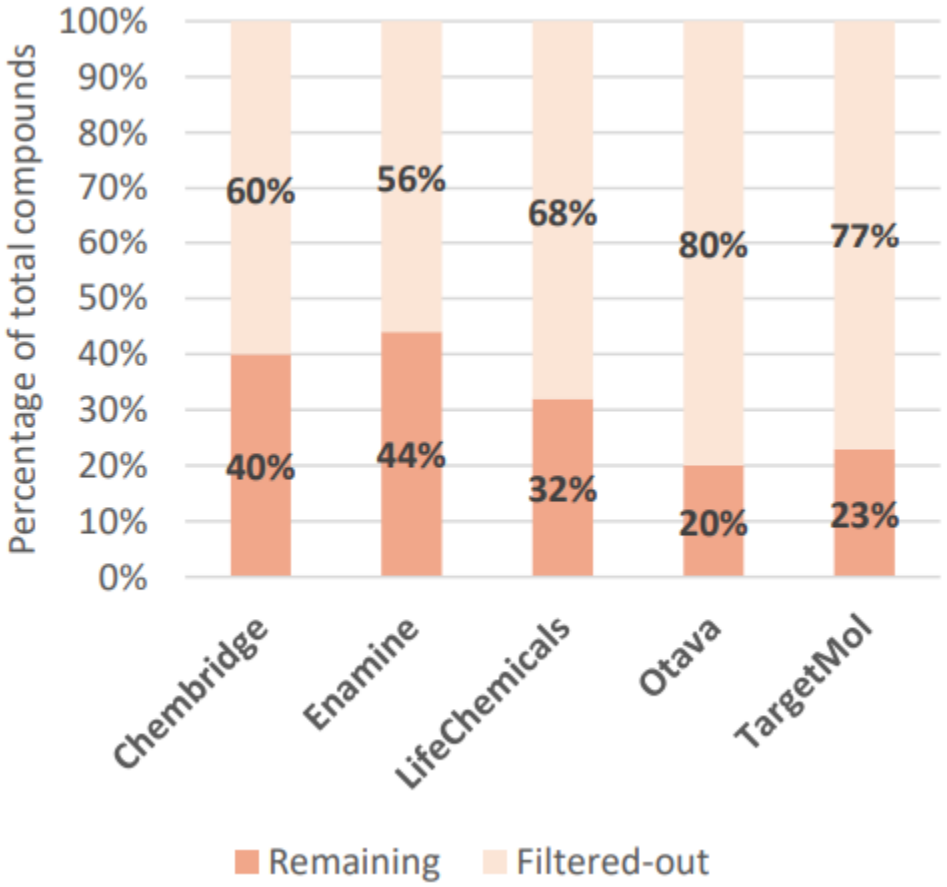
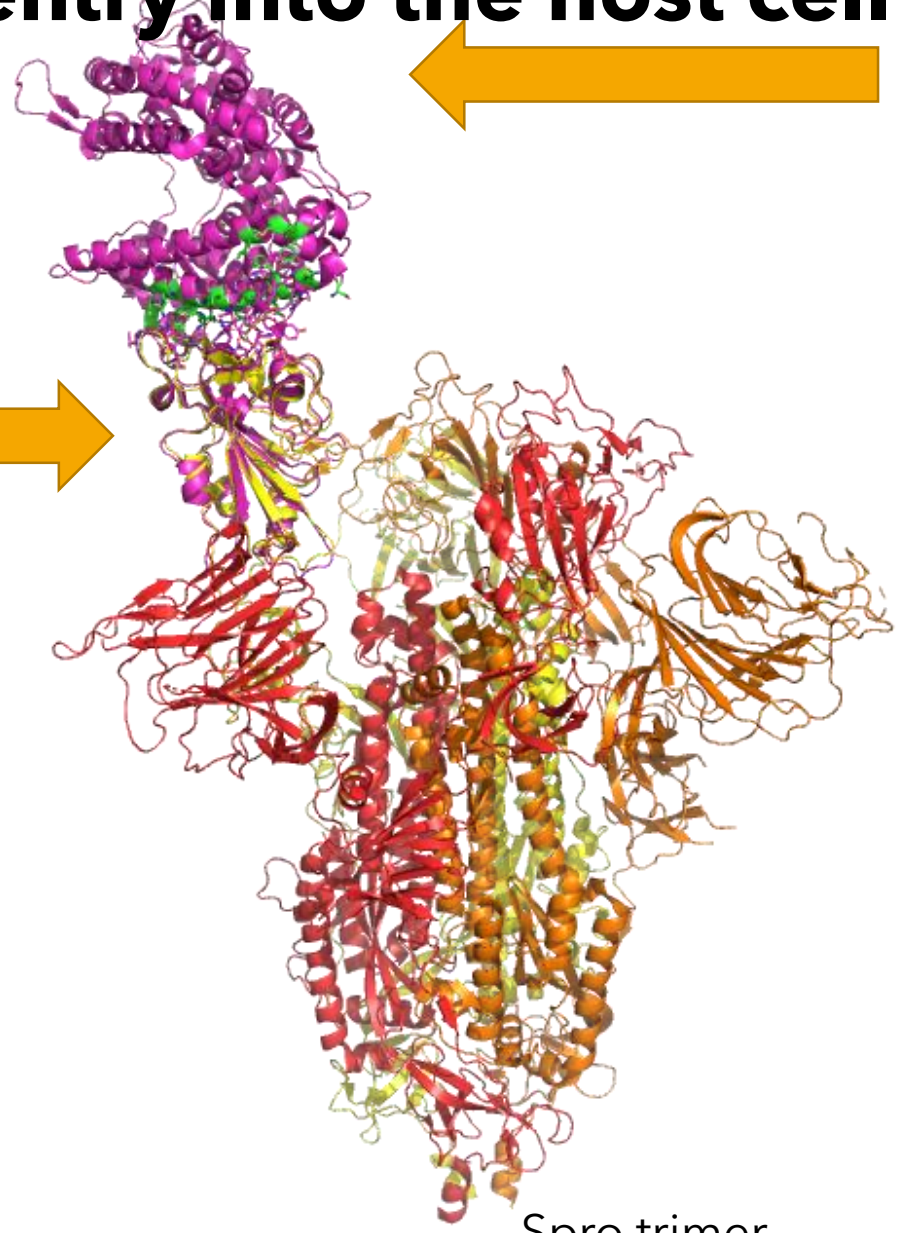


1. **Namely, vendors lack the information on the library design and the references to the primary literature.**
2. **Few references to active compounds are provided (ligand based libraries)**
3. **No receptor data, docking protocols or even references (structure based libraries)**
4. **No detailed functional group or chemical space analyses were reported**
5. **No specific orientation of the libraries toward the design of covalent or noncovalent inhibitors.**
6. **"Unfavorable" compound presence.**

Compound (relative) retention after post-filtering for REOS, PAINS, Aggregators and the Ro5.

7. Prevent virus entry into the host cell – Spike protein -S^{pro}



ACE2

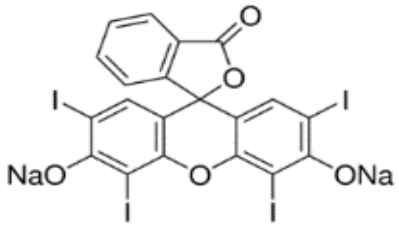
RBD – up conformation

Can this interaction be modulated?

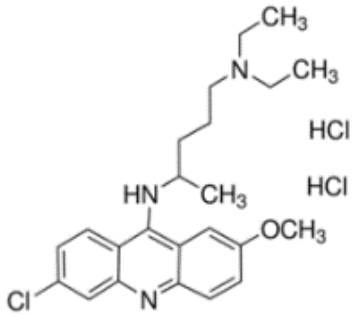
Spro trimer

7. Prevent virus entry into the host cell – Spike protein -S^{pro}

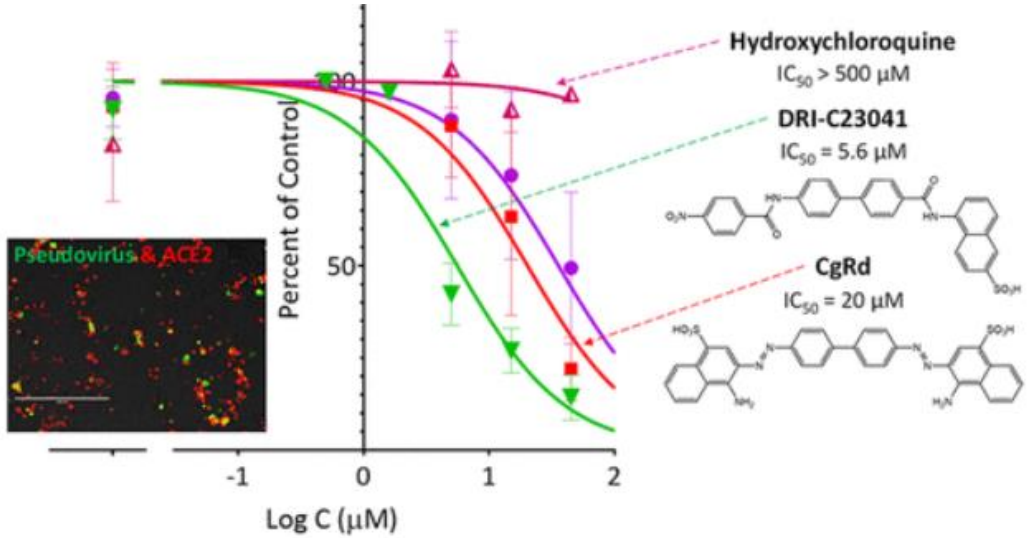
PPI approach ?



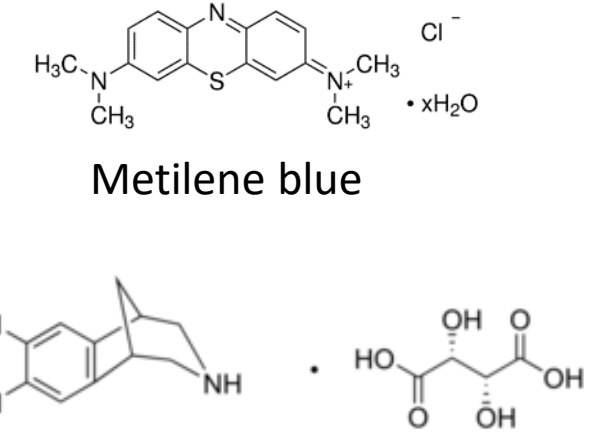
Eritrozin B



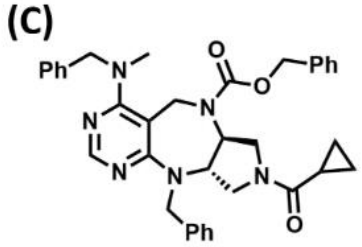
Quinacrine



DRI-C23041 (IC_{50} = 5.6 µM)

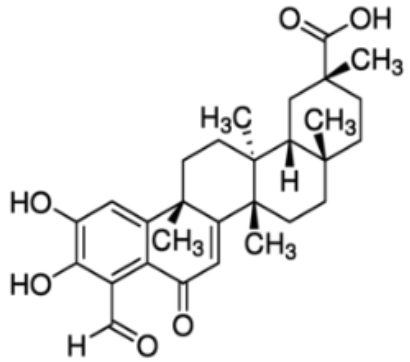


Metilene blue

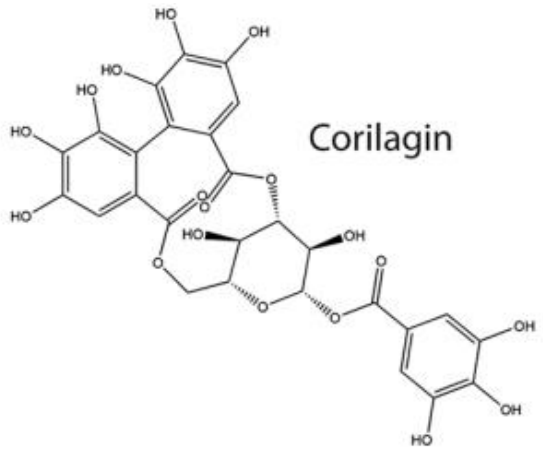


6 (SB27012)

Varenicline tartrate



Demethylzeylasteral



8. Prevent virus entry into the host cell – Study of protein-protein interfaces (S^{pro} application)

PROBLEMATICS

WHO nomenclature as of 7 June 2021	Lineage	Designation	First detected in sequence from	Status
Alpha	B.1.1.7	VOC-20DEC-01	UK	VOC
Beta	B.1.351	VOC-20DEC-02	South Africa	VOC
Gamma	P.1	VOC-21JAN-02	Japan ex Brazil	VOC
	B.1.1.7 with E484K	VOC-21FEB-02	UK	VOC (non UK)
Delta	B.1.617.2	VOC-21APR-02	India	VOC
Zeta	P.2	VUI-21JAN-01	Brazil	VUI
Eta	B.1.525	VUI-21FEB-03	UK	VUI
	B.1.1.318	VUI-21FEB-04	UK	VUI
Theta	P.3	VUI-21MAR-02	Philippines	VUI
Kappa	B.1.617.1	VUI-21APR-01	India	VUI
	B.1.617.3	VUI-21APR-03	India	VUI
	AV.1	VUI-21MAY-01	UK	VUI
	C.36.3	VUI-21MAY-02	Thailand ex Egypt	VUI
Epsilon	B.1.427/B.1.429			Monitoring

Delta Plus (B.1.617.2.1/(AY.1) is a variant of Delta, it is also treated as a variant of concern – Delta plus K417N +omicron + …

8. Prevent virus entry into the host cell – Study of protein-protein interfaces (S^{pro} application)

PROBLEMATICS

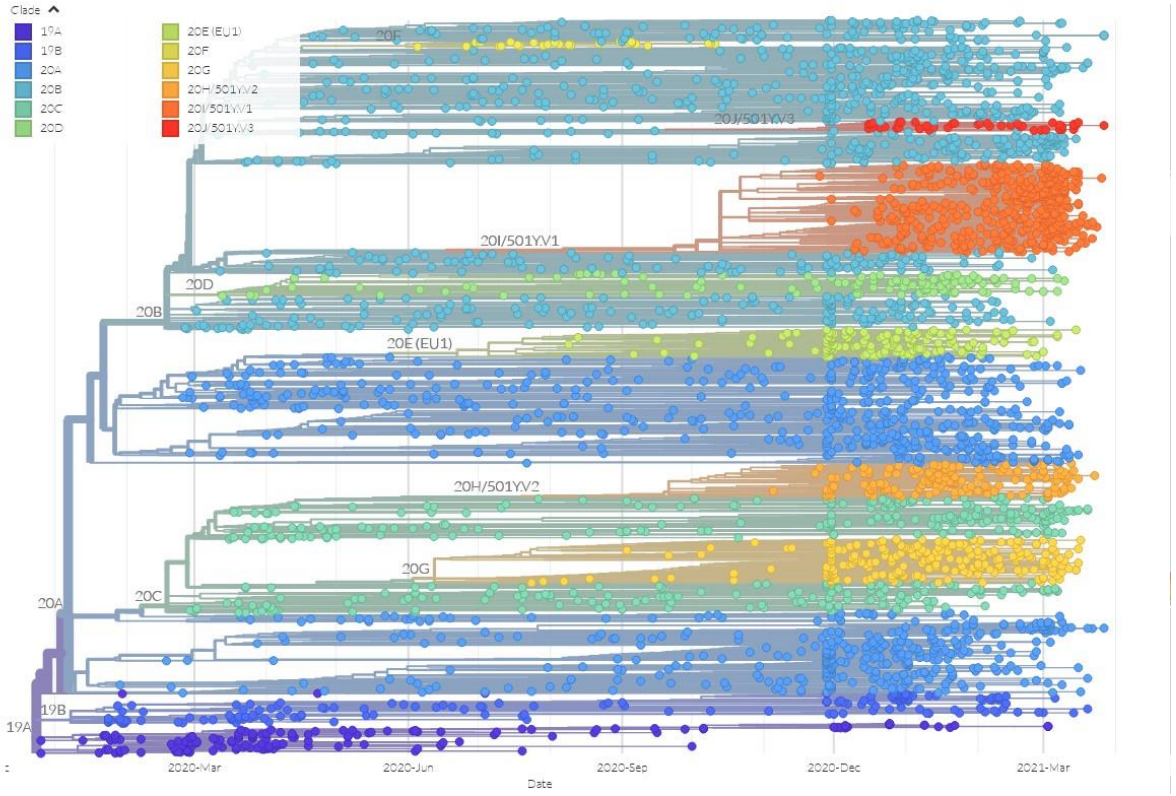
Variant [1]	*alternative name*	*Sprot/all mutations*	*Key mutations*	*Comment*
B.1.1.7	UK Variant	8/23	E69/70 del 144Y del **N501Y** (RBD interface) A570D P681H	higher transmissibility
B.1.351	South African Variant	9/21	K417N (RBD) E484K (RBD) **N501Y** (RBD) orf1b del	escape host immune response
P.1	Brasil Variant	10/17	K417N/T (RBD) E484K (RBD) **N501Y** (RBD) orf1b del	under research
B.1.617	Indian Variant	7/23	G142D E154K **L452R (RBD)** **E484Q (RBD)** D614G P681R Q1071H	under research

[1] Other known variants are COH.20G, S Q677H (Midwest variant) and L452R, B1429; reference https://www.uniprot.org/uniprot/P0DTC2

RBD-PPI

8. Prevent virus entry into the host cell – Study of protein-protein interfaces (S^{pro} application)

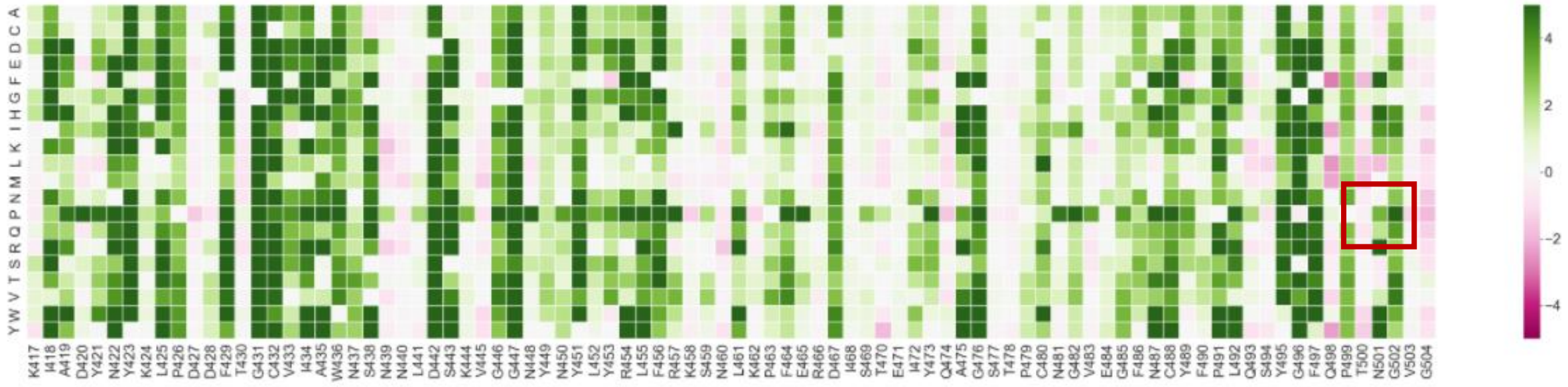
PROBLEMATICS



- The emergence of SARS-CoV-2 in late 2019 was followed by a period of evolutionary stasis
- Since late 2020 - emergence of sets of mutations – focus SARS-CoV-2 spike protein - primary antigen
- Under investigation because viral mutations can impact transmissibility and antigenicity
- Alarming evidence of reduced neutralization of some SARS-CoV-2 variants (even post vaccination)

8. Prevent virus entry into the host cell –
Study of protein-protein interfaces (S^{pro} application)

Full RBD 417-505 mutagenesis study using FoldX in order to asses these key mutations and their effect on the stability of the system, in total 1780 point mutations



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Thank You for your attention.