Design of Elaborated Binders for SARS-CoV-2 Nsp13

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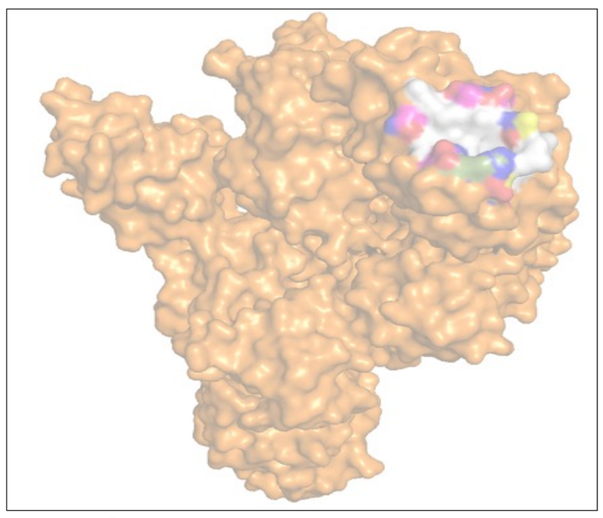
Introduction

- The SARS-CoV-2 Nsp13 is an important enzyme for viral replication and transclocation of the COVID-19 [1].
- Hence, Nsp13 has been identified as a target for antivirals [2].
- There is “C-terminus-B” a potential target site on Nsp13 where inhibitor can bind and inhibit the helicase translocation.



The C-terminus-B in top-right with different colours

Aims & Objectives

The aim of this study was to design a drug molecule that inhibit Nsp13 translocation mechanism by targeting ‘C-terminus-B’.

Materials and Methods

Fragment selection — Fragments from fragment screening were selected for small modifications.

Model of Nsp13 adopted from The Protein Bank

Fragment modification — **Molecular geometry of inhibitors constructed** using ChemDraw 21.0.0 (n= 23)

Docking analysis — **Docking** using SMINA

Analysis of docked complex (n= 1,071) → **Polar interactions visualized** using PyMOL

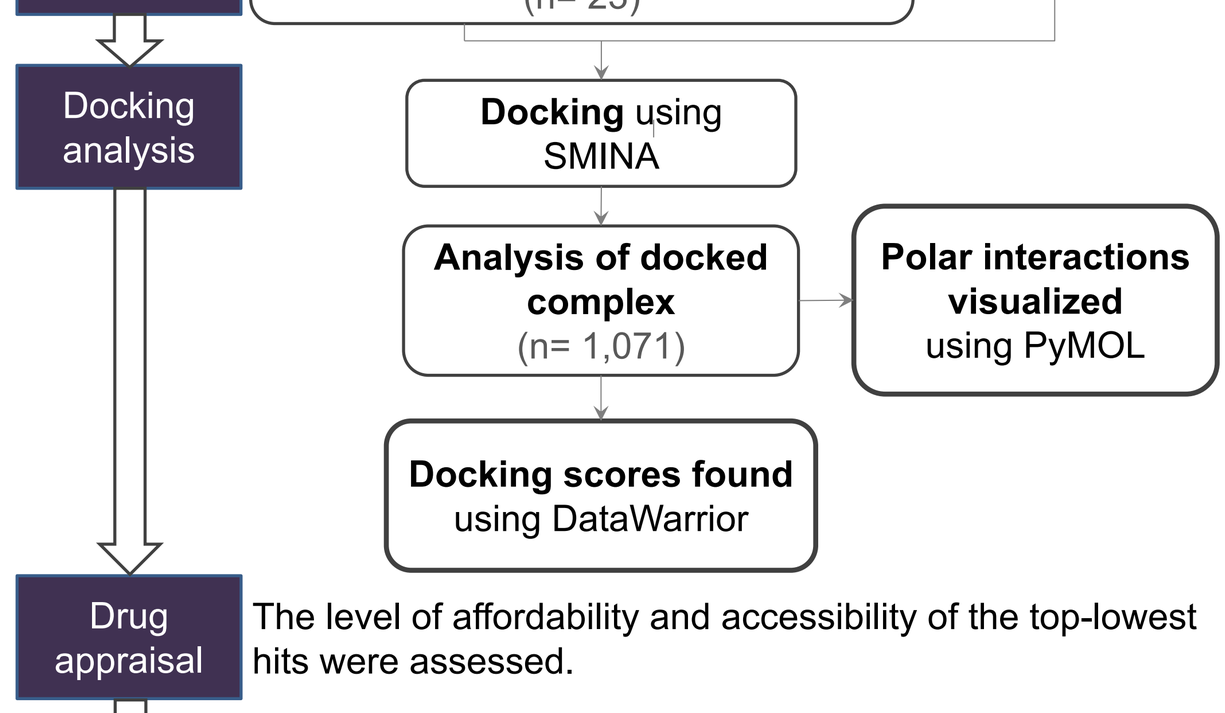
Docking scores found using DataWarrior

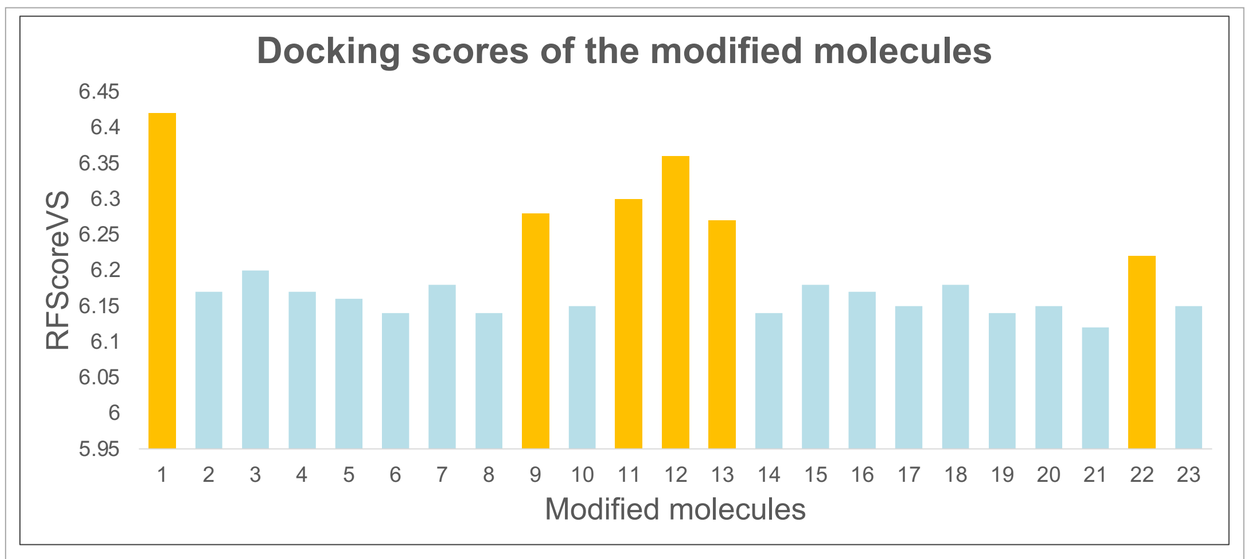
Drug appraisal — The level of affordability and accessibility of the top-lowest hits were assessed.

Further fragment mining — Searched for other motifs with higher accessibility.

Results

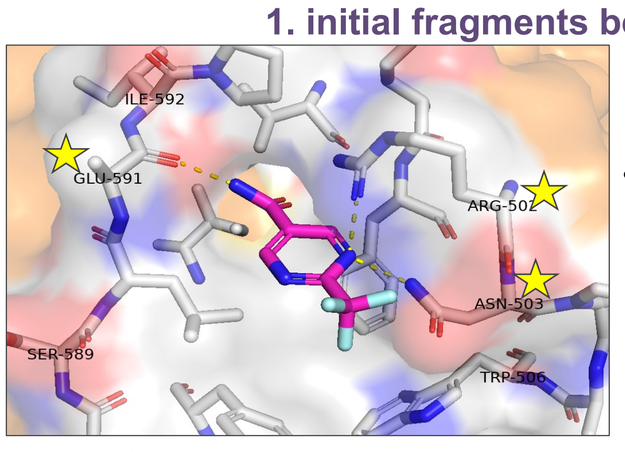
Example modifications to the fragment (“5RM9”):





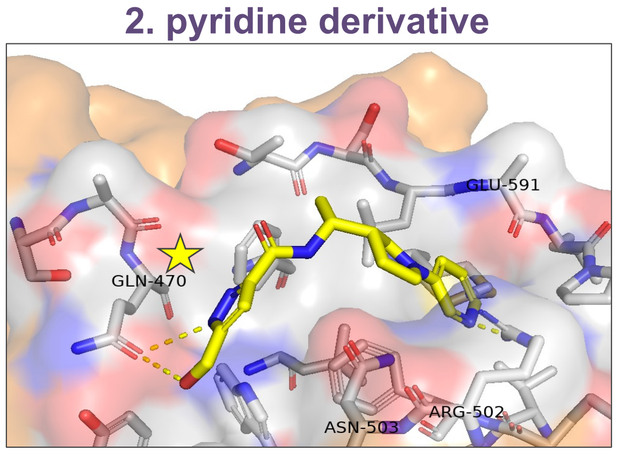
- The yellow bars are the molecules with high docking scores.
- The yellow bars are nitro derivatives on the phenyl moiety.
- Molecules 1, 9, 12 are pyridine motifs.
- Molecules 11, 13, 22 are N-oxide motifs.

1. initial fragments before modification

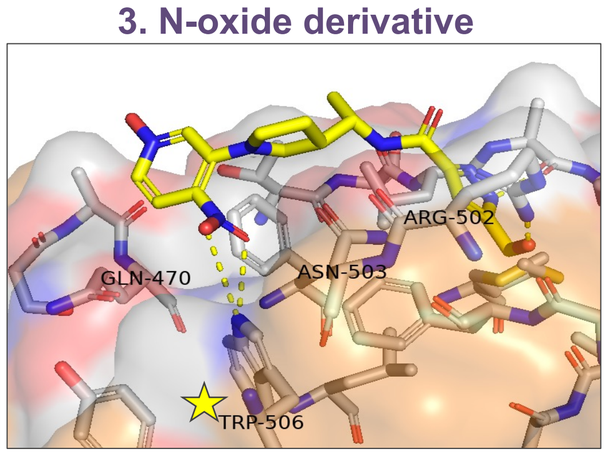


- The initial fragments made polar contacts to **Asn503**, **Arg502**, **Glu591**, and **Val495**.

2. pyridine derivative

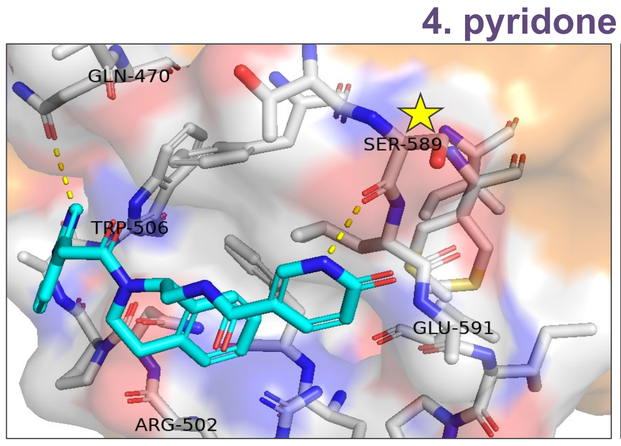


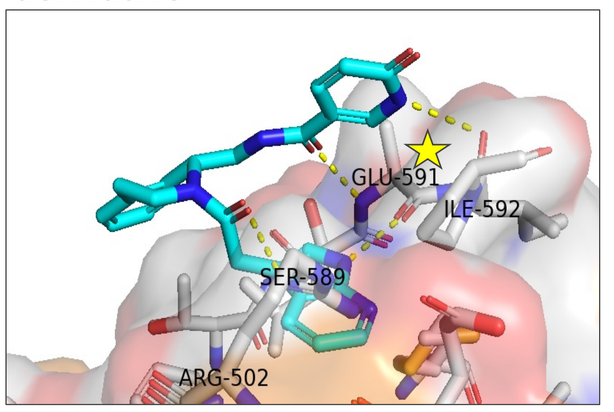
3. N-oxide derivative



- Pyridine and N-oxide derivatives made polar contacts to Asn503, Arg502, Glu591, Val495, **Trp506** and **Gln470**.

4. pyridone derivative





- Pyridone derivatives made polar contacts to Asn503, Arg502, Glu591, Val495, Trp506, Gln470, **Ser589** and **Ile592**.

The nitro derivative on the phenyl moiety has been identified as a potential inhibitor of the SARS-CoV-2, typically the N-oxide and pyridine because they made made higher docking scores than the initial fragment clusters and other minor modifications. However, because the N-oxides have low accessibility, pyridones were found as an alternative. Pyridones made similar polar interactions with the N-oxides scaffolds.

Conclusion

Pyridones can be key pharmacophore for antiviral activity. Limitation of this study is that the differences in docking scores are not significant enough to say which scaffold docks better although the nitro derivatives gave top-lowest scoring hits. More complex fragment designing needs to be done with many more functional groups.

References:
1. Newman, J.A., et al., *Structure, mechanism and crystallographic fragment screening of the SARS-CoV-2 NSP13 helicase.* Nat Commun, 2021. **12**(1): p. 4848.
2. White, M.A., W. Lin, and X. Cheng, *Discovery of COVID-19 Inhibitors Targeting the SARS-CoV-2 Nsp13 Helicase.* J Phys Chem Lett, 2020. **11**(21): p. 9144-9151.