REAL Fragment Library: efficient fragment growing and linking inside Enamine REAL

A. Kapeliukha[1], R. Gaidar[1], O.Semenenko[1], M.Protopopov[1], O. Tarkhanova[1], Y. Moroz[2]

[1]Chemspace LLC, 85 Winston Churchill Street, Kyiv 02094, Ukraine
[2]Enamine Ltd, 78 Winston Churchill Street, Kyiv 02094, Ukraine

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Introduction

Fragment-based drug discovery is a powerful method for identifying promising starting points for new drugs, but growing fragments into lead compounds is often challenging. This problem can be solved using commercially accessible combinatorial chemical spaces like Enamine REAL, which offers 2.7T molecules at a competitive price. Due to the modular nature of this space, all its structural elements can be annotated in terms of the growth vectors they contain, thus enabling the creation of focused chemical spaces.

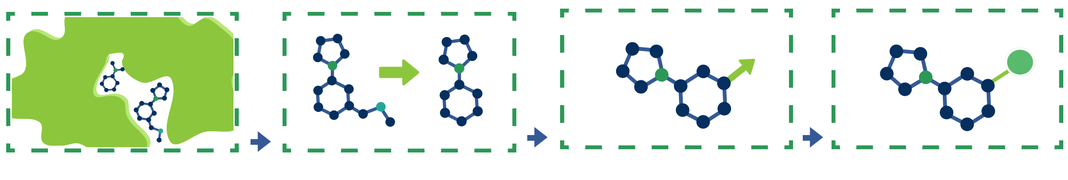
In this work, we propose a workflow to grow fragments inside Enamine REAL and show the potential of this approach using examples from the Nsp3 macrodomain of SARS-CoV-2. We also propose REAL Fragment Library – a pre-plated set that is the perfect entry point to Enamine REAL and efficiently covers the REAL synthon space.

Approach Overview

Depending on the number of fragments in the crystal structure, it is possible to employ both fragment growing and fragment linking strategies.

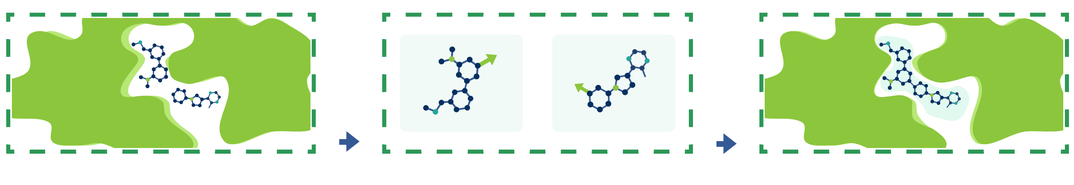
Fragment Growing

1



- Generation of Murcko scaffold
- Selection of exit vector
- Design of custom space
- Evaluation of molecules using docking

2



- Generation of custom spaces for both fragments
- Docking into the protein using an APF template

REAL Fragment Library

To efficiently grow fragments inside Enamine REAL we designed REAL Fragment Library - a pre-plated fragment collection that efficiently covers the chemical space of all synthons inside the REAL Space.

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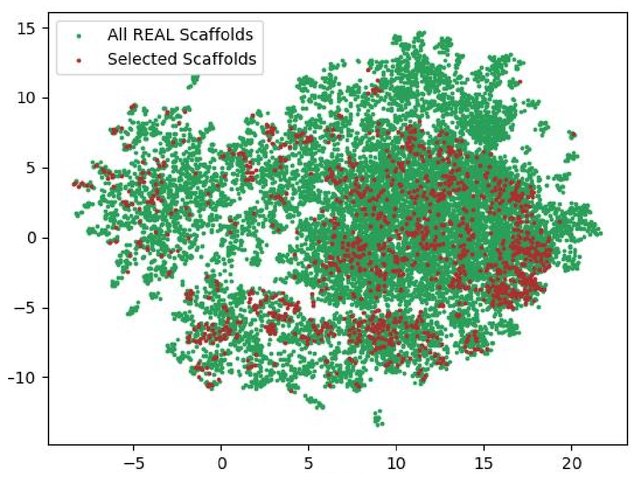
Coverage of REAL Murcko scaffolds



- Pre-plated library
- Contains sociable scaffolds
- High coverage of REAL scaffolds
- Minimal pharmacophore diversity
- Cherry-picking available

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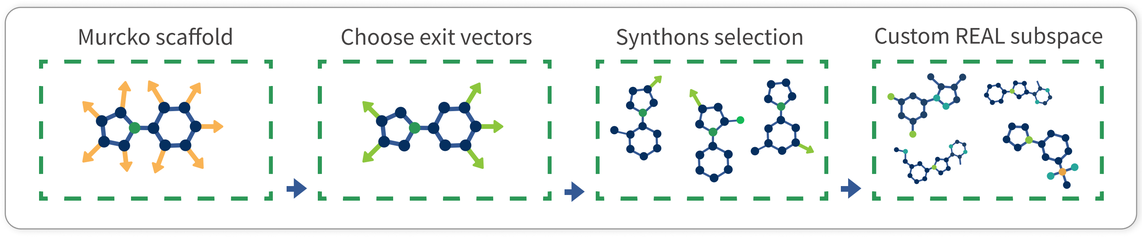
Design of custom REAL subspaces

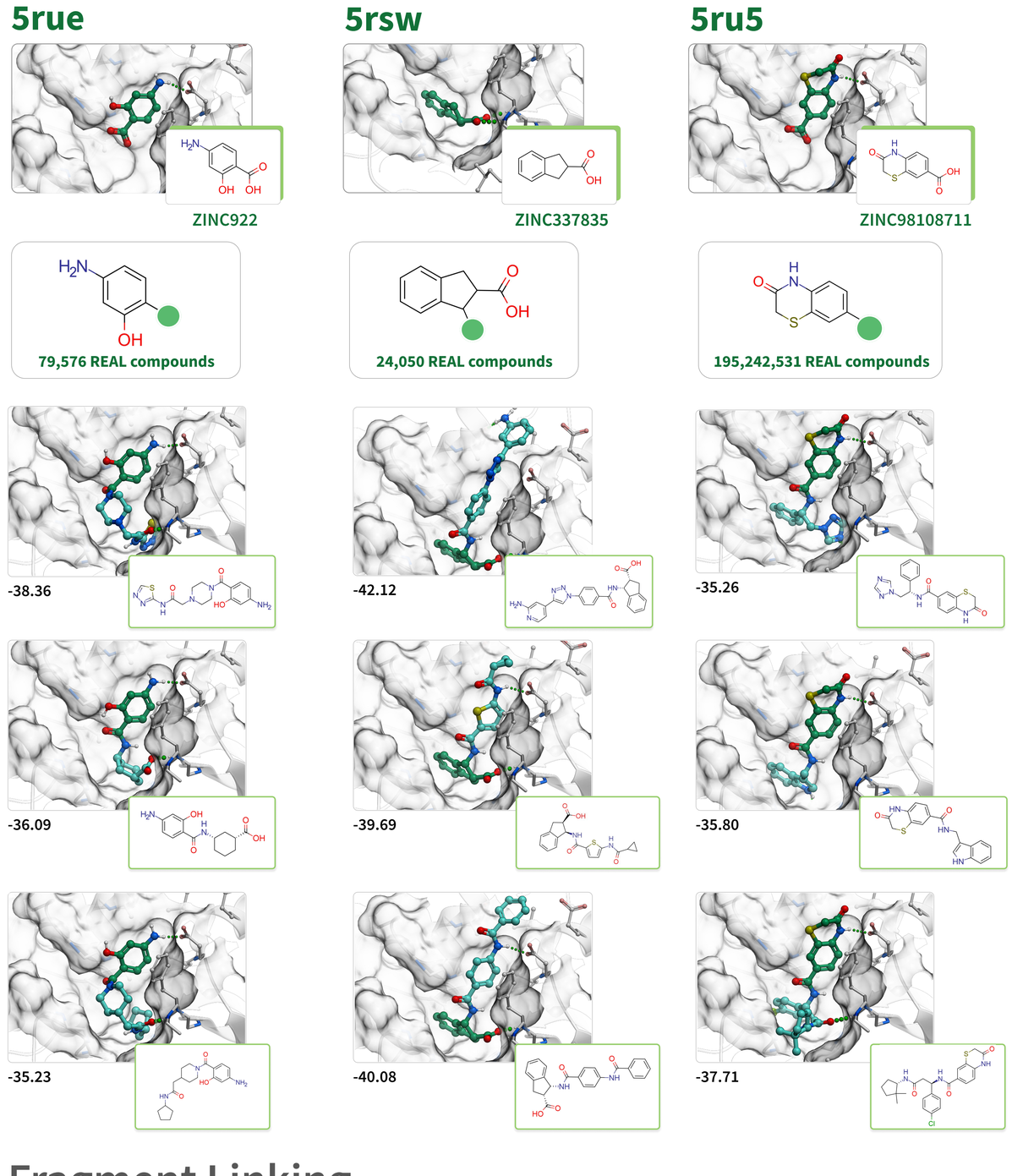


- High synthetic feasibility
- Control over physicochemical properties
- Perfect for computational exploration
- Simplified SAR investigation

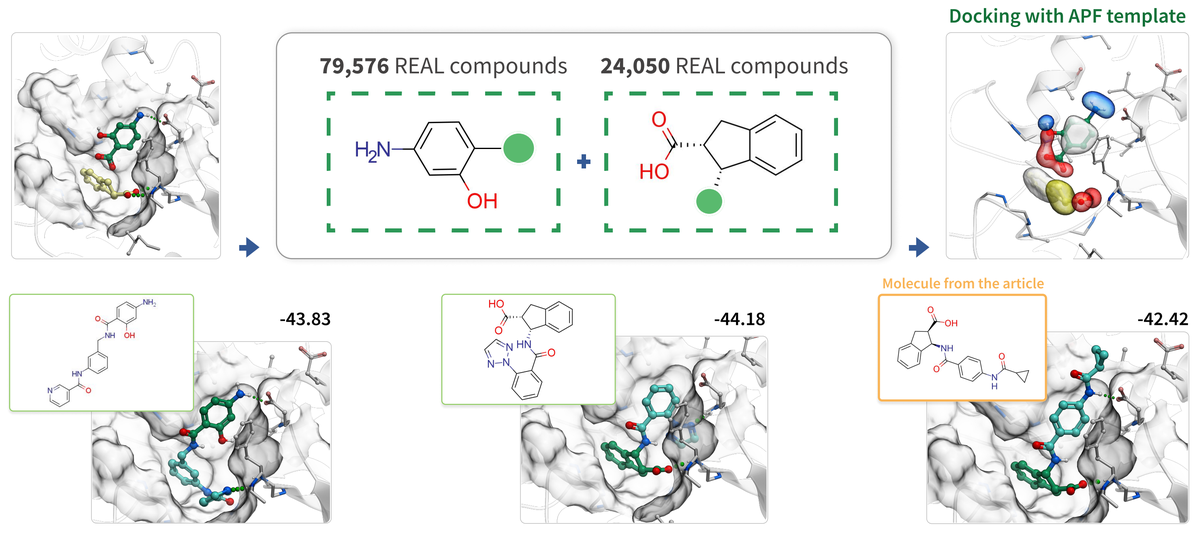
Case Example

To showcase the ability of the proposed approach to efficiently link and grow fragments we applied it to the fragments discovered in the article on the design of binders for Nsp3 macrodomain of SARS-CoV-21. As a result, we successfully found full molecules with good docking scores for each of the fragments*. After the fragment linking workflow, we were additionally able to find the exact molecules discovered in the article.

Fragment Growing



Fragment Linking



* The docking was performed using ICM Pro software provided by MolSolf. The docking scores are provided for the corresponding molecules.

References: Schuller, M., Correy, G. J., Gahbauer, S., et al. "Fragment binding to the Nsp3 macrodomain of SARS-CoV-2 identified through crystallographic screening and computational docking," Science Advances, V. 7, No. 16, 2021.