Towards the De Novo Design of HIV-1 Protease Inhibitors Based on Natural Products

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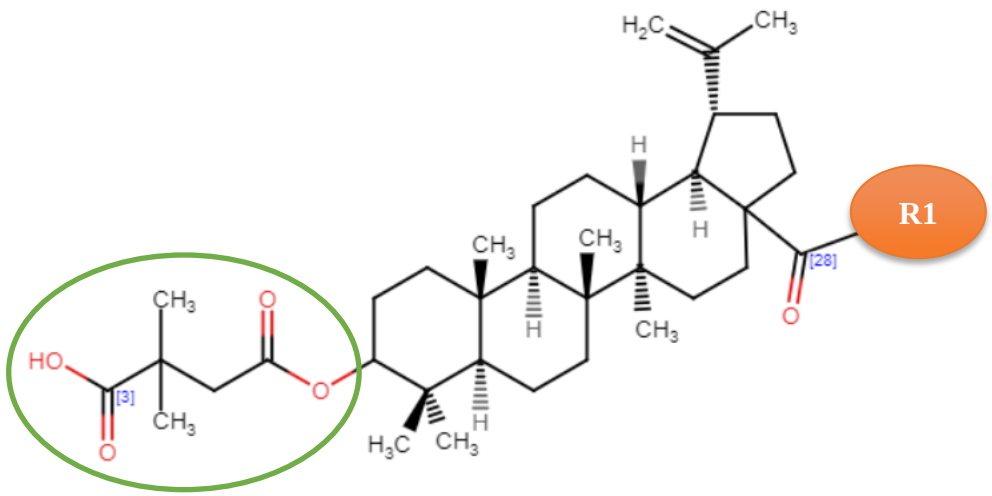
Objective

The goal of this work was to developed a virtual focused compound library of HIV-1 protease inhibitors from natural products fragments through de novo design.

Pharmacophore at C-3 is crucial



- Amine at C28 is favorable.
- Ester at C-28 is not favorable.
- Methylene at C-28 is not favorable.
- Cyclic secondary amine moiety (piperazine or piperidine) at C-28 remarkably increases activity.

Template for building computationally new chemical compounds analogs to Bevirimat

Enamine

COCONUT
COllection of Open Natural ProdUcTs

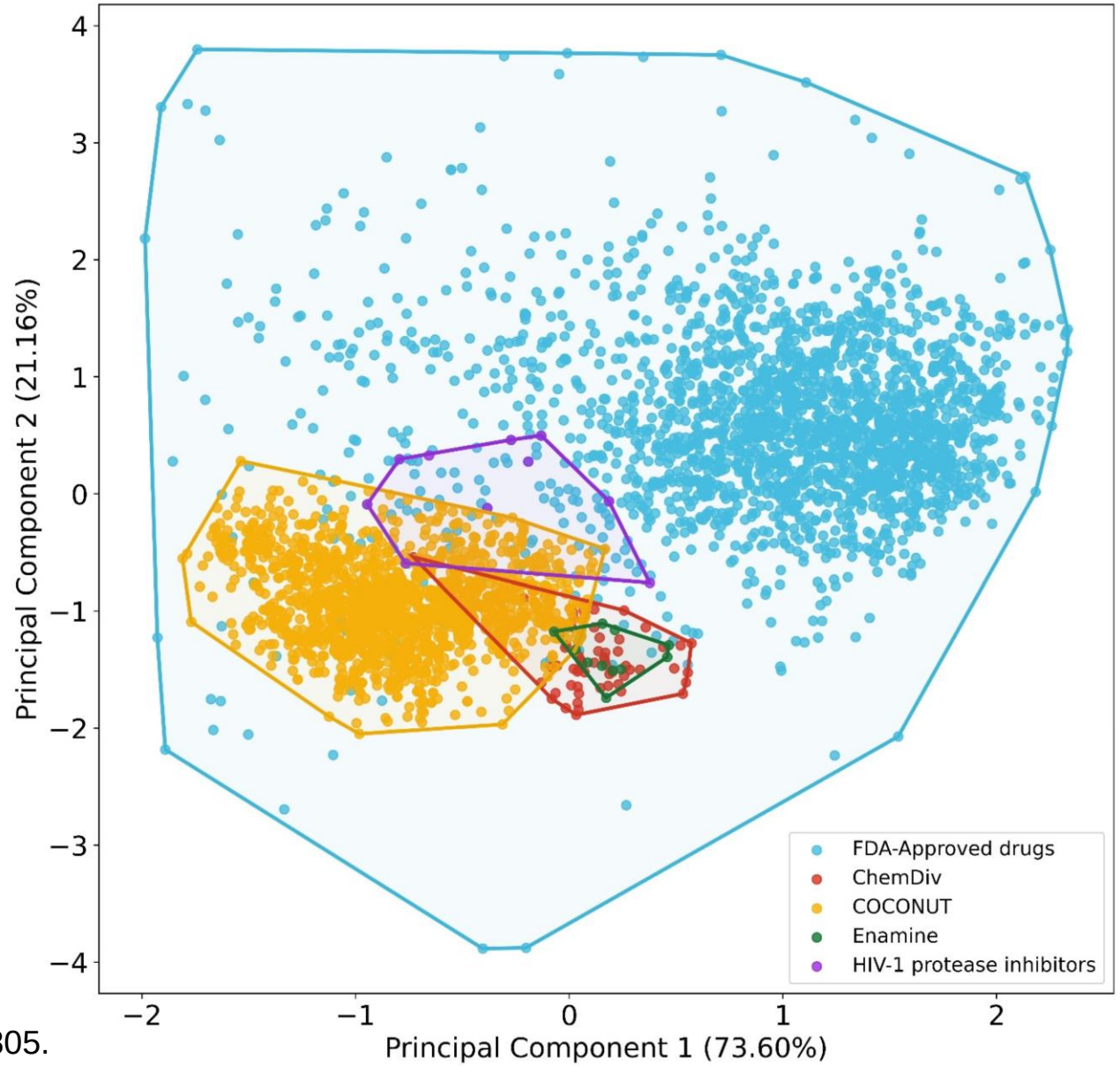
Lazerwith, S.E.; Siegel, D.; McFadden, R.M. et al. 5.19 - New Antiretrovirals for HIV and Antivirals for HBV. In; Chackalamannil, S., Rotella, D., Ward, S.E.B.T.-C.M.C.I.I.I., Eds.; Elsevier: Oxford, 2017; pp. 628–664

Chemical Space PCA

Lipinsky and Veber rules:

- HBA ≤ 10
- HBD ≤ 5
- LogP ≤ 5
- MW ≤ 500
- RB ≤ 10
- TPSA ≤ 150

COCONUT compounds generated were the most diverse vs ChemDiv and Enamine compounds.



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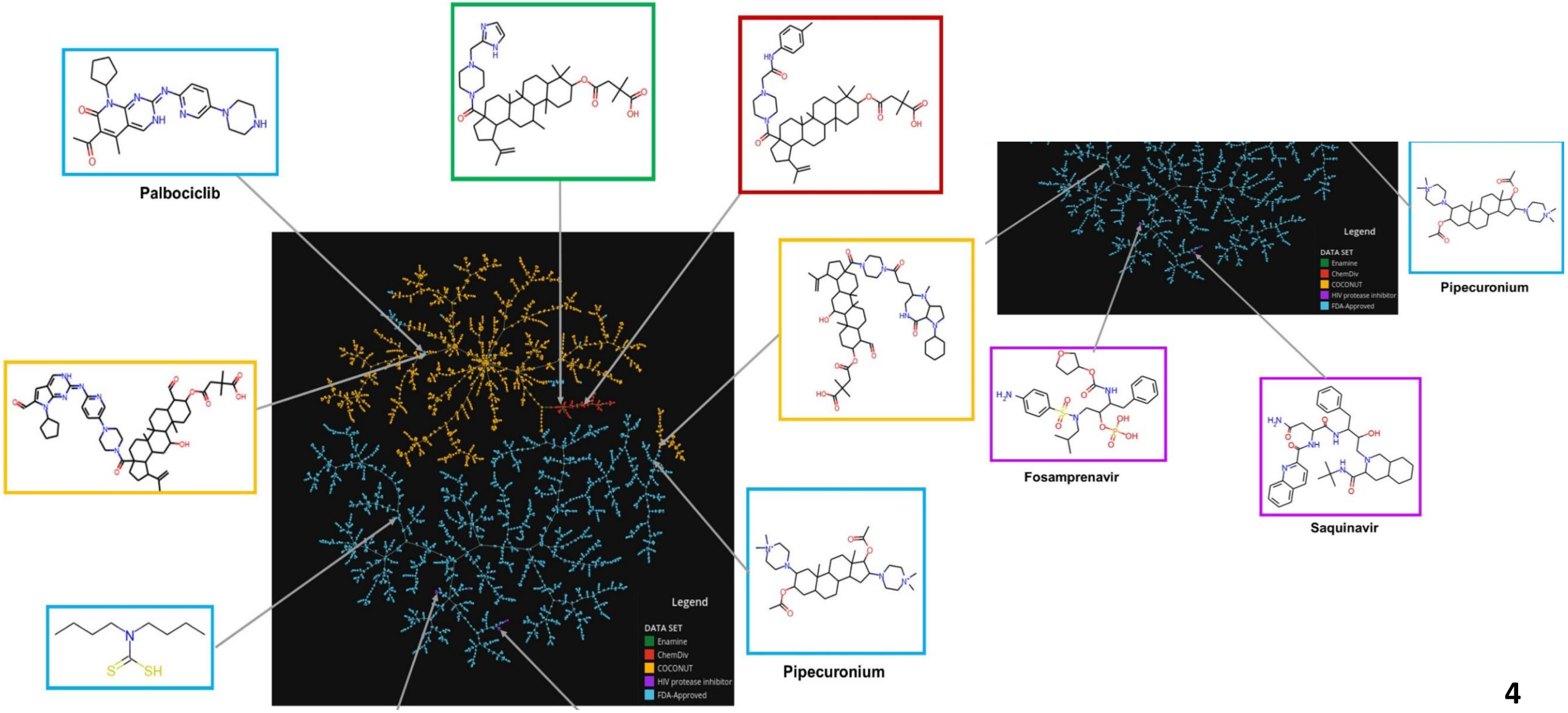
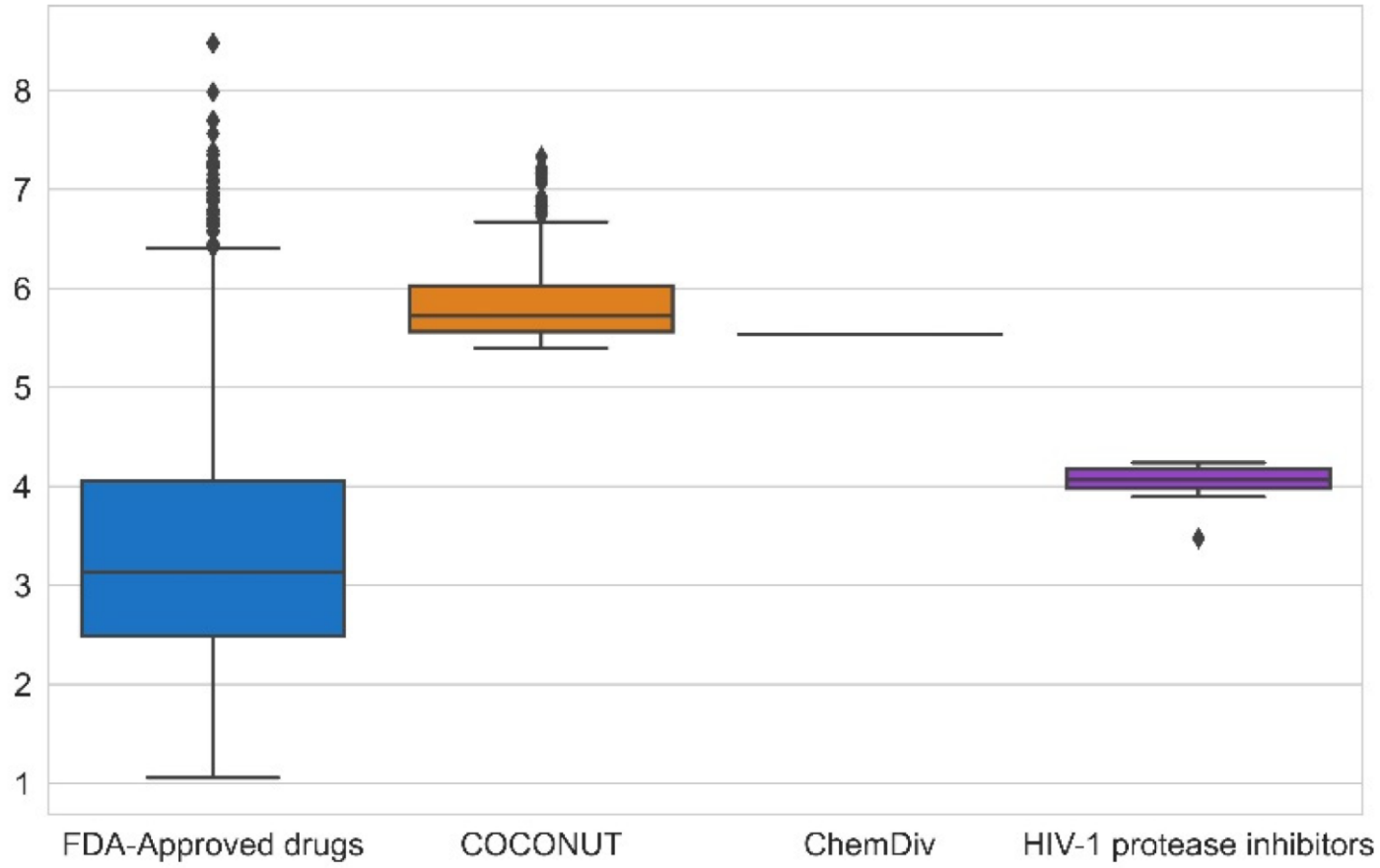
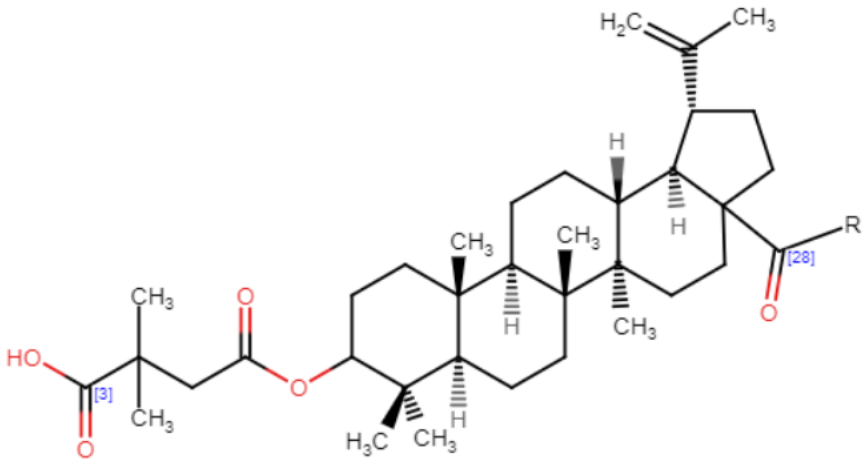
Chemical Space TMAP using ECFP-4 1024 bits



Synthetic feasibility





251 compounds generated from COCONUT fragments had physiochemical properties similar to HIV-1 protease inhibitors approved by FDA and synthetically viable (SA<6).

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ADME/Tox profile (*in silico)*

Absorption → 67% HIA like FDA HIV inhibitors; consensus LogP 5.7>FDA-HIV (3.5)
Good absorption in the human intestine but are not suitable for oral administration.

Distribution → blood-brain barrier (BBB) permeability like FDA HIV inhibitors

Metabolism → No CYP3A4 inhibitor
not lead to adverse drug effects because of drug-drug interaction
→ No CYP2C9 inhibitor
contributes to drug metabolism.

Excretion → 25% COCONUT compounds generated (low excretion)

Toxicity → No hepatotoxicants

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Conclusions

COCONUT: 1534 -→251 (16%)

- Physicochemical properties like FDA HIV-1 protease inhibitors.
- Easy synthesizable.
- The most diverse compounds vs (ChemDiv or Enamine databases).

ADMET/Tox profile

- Good absorption in the human intestine, high lipophilicity (not suitable for oral administration).
- metabolizable, no hepatotoxicants, but low excretion.

We propose a general protocol to built compounds analogous to Bevirimat.

biomolecules

MDPI

Article

Towards the De Novo Design of HIV-1 Protease Inhibitors Based on Natural Products

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Abstract: Acquired immunodeficiency syndrome (AIDS) caused by the human immunodeficiency virus (HIV) continues to be a public health problem. In 2020, 680,000 people died from HIV-related causes, and 1.5 million people were infected. Antiretrovirals are a way to control HIV infection but not to cure AIDS. As such, effective treatment must be developed to control AIDS. Developing a drug is not an easy task, and there is an enormous amount of work and economic resources invested. For this reason, it is highly convenient to employ computer-aided drug design methods, which can help generate and identify novel molecules. Using the de novo design, novel molecules can be developed using fragments as building blocks. In this work, we develop a virtual focused compound library of HIV-1 viral protease inhibitors from natural product fragments. Natural products are characterized by a large diversity of functional groups, many sp^3 atoms, and chiral centers. Pseudo-natural products are a combination of natural products fragments that keep the desired structural characteristics from different natural products. An interactive version of chemical space visualization of virtual compounds focused on HIV-1 viral protease inhibitors from natural product fragments is freely available in the supplementary material.

Keywords: artificial intelligence; de novo design; fragment-based drug discovery; HIV-1 inhibitors; pseudo natural products

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