Rule-Based Retrosynthesis for Accessible Hits: An Open-Source Python Package

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BACKGROUND:

- Combinatorial 1 to 3-step reaction sequences can access vast new regions of chemical space

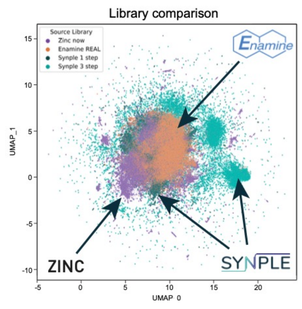
CHALLENGE:

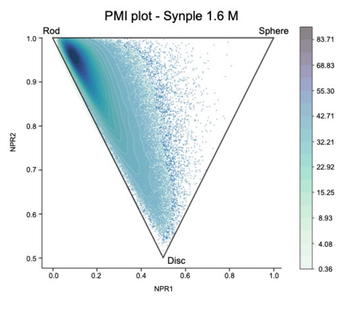
- **Determining accessibility** of virtual library or *de novo* designed compounds based on reliable reactions and available building blocks

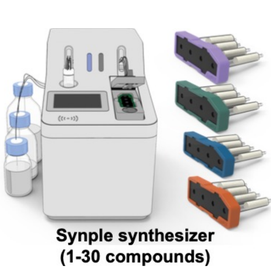
APPROACH:

- **Automated retrosynthesis** based on selected available building blocks and optimized reactions

- Synple Chem automatized reactions enable rapid synthesis of complex molecules







Any virtual compound space → **Virtual screening** → Hit candidates → **Syn-Retro** → **Rapidly Accessible hits**

10^6 - 10^9 | 10^2 - 10^4

< 10 mins

> 2 weeks

Python package

Accessible building blocks

```
awesome-chemist ~ %
prepare-bb-db --input
accessible_building_blocks.csv
```

Defined RXN SMARTS

```
awesome-chemist ~ %
validate-rxn-smarts --input
reaction_smarts.csv
```

```
awesome-chemist ~ %
run-retro --compound-list
list_of_compounds.csv
```

Syn-Retro

SCAN ME :)

ID	SMILES
NEW01	
…	…
NEW##	

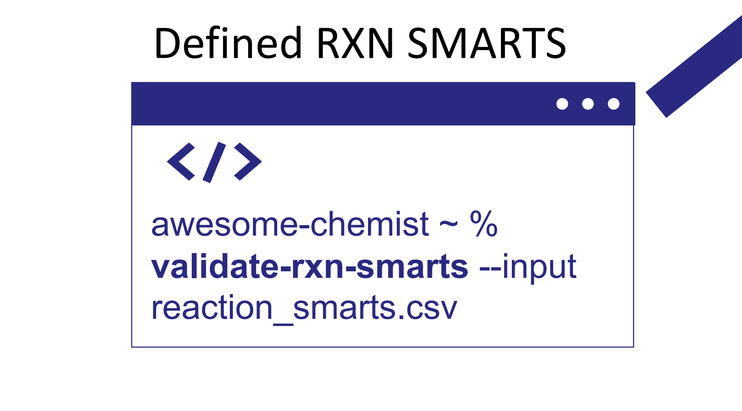
List of compounds

ID	RXN_1	RXN_#	BBs

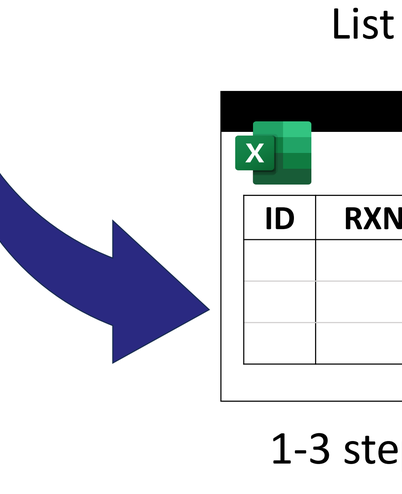
1-3 steps synthesis plans

Case Study: Retrosynthesis plans for REINVENT[3] generated molecules

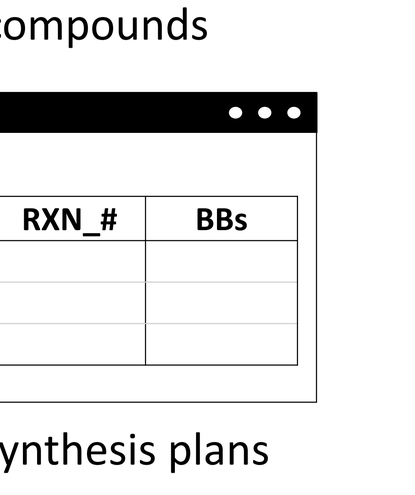
Synple-accessible examples:



Reductive amination
Boc deprotection
Amide bond formation



Reductive amination
Boc deprotection
Reductive amination



Amide bond formation
Boc deprotection
Reductive amination

References
Jiang, T., …, & Bode, J. W. (2021). An integrated console for capsule-based, automated organic synthesis. *Chemical Science*, *12*(20), 6977-6982.
McMillan, A. E., …, & Bode, J. W. (2022). A vending machine for drug-like molecules-automated synthesis of virtual screening hits. *Chemical science*, *13*(48), 14292-14299.
Loeffler, H., … , & Engkvist, O. (2023). REINVENT4: Modern AI–Driven Generative Molecule Design.

SYNPLE
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