Are we close to the **AI revolution in small molecule synthesis**? Enabling autonomous synthesis with AI agents and automation

ONEPOT.AI

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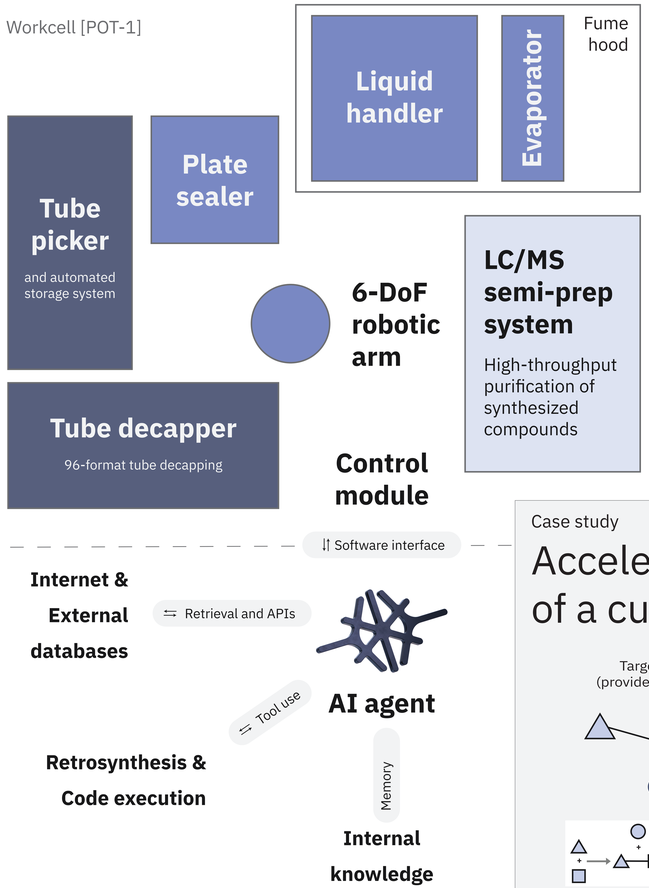
Abstract

Synthesis of small molecules is a key bottleneck in drug discovery and the main factor responsible for **extremely long cycle times** in the DMTA cycle. Development of automated strategies for synthesis would enable significant acceleration of the process, but encounters **numerous barriers** including: complex experimental setups, inability to precisely model reaction outcomes and therefore reliance on human intuition. Multiple stages of the current automated synthesis workflows require human decision making, impeding complete autonomy.

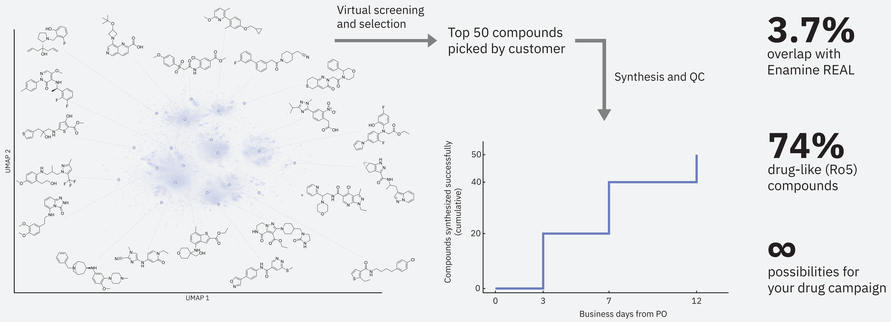
We present an **AI-enabled platform for multi-step autonomous synthesis of small molecules**. It consists of an automation setup including compound storage system, liquid handling, heating, and purification steps. The hardware is managed by AI agents that employ large language models and a set of tools to perform various research operations: reviewing literature, running calculations, analyzing experimental results. High modularity of this system enables increase in success rates by integrating ML models that predict reaction outcomes through training on large proprietary chemical reactivity datasets.

Our setup allows to rapidly iterate over experiment designs and workflows



Case study

Ultrafast synthesis of compounds from a **2.7B chemical space**



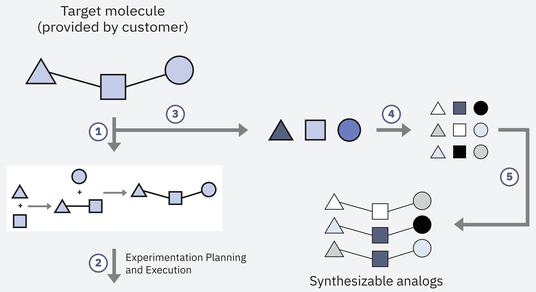
3.7% overlap with Enamine REAL

74% drug-like (Ro5) compounds

∞ possibilities for your drug campaign

Case study

Accelerated **two-step synthesis** of a custom library



1. In this case study we were given a collection of 64 compounds. Retrosynthetic analysis demonstrated that provided compounds required two-step synthesis in most of the cases.
2. For 9 molecules from the original list, valid starting materials were available. The remaining molecules consisted of fragments that were either not purchasable or had excessively long lead times.
3. Therefore, we took the following approach: for every molecule in the list that could not be synthesized, we split it into feasible fragments according to the selected reactions.
4. After determining the corresponding fragments, we searched across catalogs from different building block vendors to identify the most similar starting materials, aiming to cover the closest analogs of the required fragments.
5. Finally, the closest starting materials were cross-enumerated to reconstruct a scaffold similar to the originally provided molecule. The resulting pool of synthesizable analogs was then rescored based on their similarity to the customer's molecule.

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