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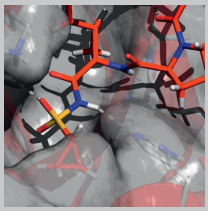

Medicinal Chemistry and Chemical Biology Highlights

Division of Medicinal Chemistry and Chemical Biology
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Accelerating Early Drug Discovery Through Automated Medicinal Chemistry

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Abstract: The discovery of new medicines relies on the iterative Design, Make, Test and Analyse (DMTA) cycle. Increasing the speed of this cycle is key to accelerating drug discovery and delivering new medicines to patients faster. As a result, pharmaceutical companies are closely monitoring and optimising their DMTA processes to increase efficiency. Over the last two decades, advances in automation have progressively transformed medicinal chemistry, enabling more efficient synthesis, purification, and profiling of new compounds. At Novartis Global Discovery Chemistry, these efforts have led to innovative capabilities such as MicroCycle, which combines microscale synthesis, automated purification, miniaturised profiling, and predictive modelling into a single platform. By generating highly information-rich datasets from minimal material consumption, MicroCycle accelerates decision-making while supporting sustainable drug discovery practices. A major recent advance has been the adaptation of magnetic bead technology from biology to organic synthesis, addressing one of the longstanding challenges of automated medicinal chemistry: the efficient execution of multistep synthetic sequences in miniaturised, plate-based formats. By enabling the automated synthesis of complex molecules and expanding the accessible chemical space to high-throughput workflows, magnetic beads represent a transformative advance in the way chemical matter is explored and optimised. Together, these innovations illustrate how automation, data generation, and machine learning are reshaping medicinal chemistry and paving the way towards increasingly autonomous, AI-enabled discovery laboratories.

Keywords: Automated medicinal chemistry · Data foundation · DMTA cycle · Magnetic solid phase synthesis · Microscale chemistry

1. Introduction

Medicinal chemistry is a wonderful journey aimed at identifying molecules with the highest chances of becoming new medicines to treat patients and to improve their lives. At its core lies the Design, Make, Test and Analyse (DMTA) cycle, an inherently iterative process. Each step in this cycle can require considerable time, resources, and expertise. As a result, accelerating the DMTA cycle has become a major objective across the pharmaceutical industry, enabling faster delivery of medicines to patients, while allowing medicinal chemists to focus on challenging scientific questions where human creativity and judgment are key.[1-4]

Since the combinatorial chemistry era in the early 2000s, Global Discovery Chemistry (GDC) has continuously invested in the automation of recurrent tasks such as synthesis, purification and analytical characterisation. These efforts have led to the development of integrated platforms designed to improve efficiency, data generation, and decision making in early drug discovery and, as described in the contributions highlighted here, to push the boundaries of what automation can achieve.

2. Automated Platform; MicroCycle

In 2018, a research proposal led by a team of Novartis scientists postulated that bringing together the entire medicinal chemistry process onto a single platform would deliver substantial acceleration, not only by co-location of processes, but by integrating microscale chemistry, automated purification, *in situ* quantification, miniaturised profiling, and predictive models within one platform.[5] The proposal was awarded and platforms were built; one platform in Basel and one in Cambridge, MA.

MicroCycle has been optimised to use a very limited amount of scaffold. Less than 80 mg of a small molecule scaffold is required. The same quantity would traditionally be used for the synthesis of a single compound. From this, a 96-well plate of products is generated at 4 µmol scale, which are purified and profiled for potency in collaboration with the project team and for physicochemical properties on the MicroCycle platform. Thanks to the miniaturisation of our profiling, only 30 µL (10 mM) DMSO stock solution is needed for a full absorption, distribution, metabolism and excretion (ADME) profiling including HT solubility, LogD, liver microsomal clearance (mouse, rat, human) and MDCK-LE (Madin-Darby canine kidney cells- Low Efflux) permeability. Therefore, with only 80 mg of scaffold, a physicochemical and potency data set of 672 data points can be generated. Such a density of information per milligram of starting material is to our knowledge unmatched in routine medicinal chemistry (Fig. 1).

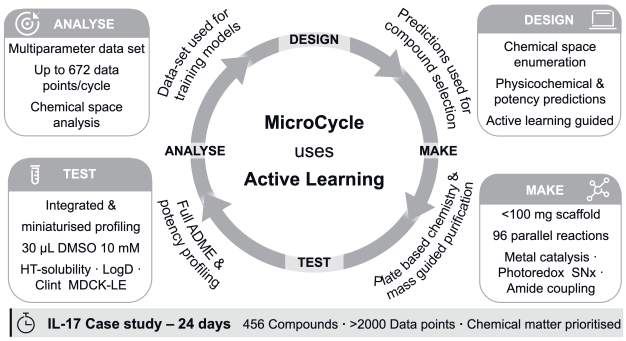

Fig. 1. The MicroCycle platform; a closed loop DMTA cycle built in Global Discovery Chemistry, Novartis.

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This platform is a powerful tool for generating the data foundation that feeds our predictive models, which guide the designs of the subsequent compound library iterations. Library design generally starts with the enumeration of the chemical space around a given scaffold by varying a synthetic handle through a desired chemistry transformation using a large set of building blocks. Predictions of physicochemical properties and potency against the desired target are then generated for each compound, enabling data driven prioritization of compounds for the next DMTA iteration. These iterative cycles enable active learning; every iteration's dataset is used to retrain the models, sharpening predictions with each cycle. The power of this approach is illustrated by S. Racine and colleagues, who applied MicroCycle to evaluate a novel thiazole-based series for the Interleukin-17 project in just 24 days.[6] In this showcase, matrix libraries were performed starting from six scaffolds featuring distinct central core motifs, using a constant set of 96 building blocks to enable direct comparison across chemotypes. The efforts led to a collection of 456 isolated compounds from 576 planned. A rich data collection of more than 2,000 data points was collected. Analyses of the resulting chemical space with respect to target affinity and physicochemical properties enabled clear prioritisation of the central core and identification of high-value capping groups. This campaign exemplifies what MicroCycle was built for: rapid, sustainable and robust exploration of chemical space in a real-world drug discovery context.

3. Solving the Multistep Challenge with Magnetic Beads

As powerful as MicroCycle is, it operates within a defined space; each run is optimised for a single chemical transformation applied uniformly across a 96-well plate or at most, two transformations when a deprotection step is included. Metal-catalysed and photoredox reactions, nucleophilic substitutions, reductive aminations, Mitsunobu reactions, amide couplings and many other transformations are readily enabled. However, the automated synthesis of multistep libraries remained an unsolved challenge.

Recently, this limitation has been elegantly addressed by P. Meier and coworkers, who successfully revisited a tool familiar to biology laboratories: magnetic beads.[8] They adapted it to the demands of miniaturised and automated organic synthesis. They engineered polystyrene-coated magnetic particles that retain the swelling behaviour of traditional solid phase resin in organic solvents, while incorporating a ferromagnetic core that fundamentally transforms how solid support can be handled.

The overall workflow is straightforward yet powerful. Starting materials are immobilized on the magnetic beads, and each reaction step proceeds similarly to a traditional solid phase synthesis. The innovation becomes apparent in the subsequent steps: upon application of a magnetic field beneath the plate, the beads sediment within seconds, allowing automated aspiration of the supernatant containing excess reagents, by-products, and impurities. No filtration, centrifugation, or manual intervention is required. The resulting intermediate is immediately ready for the next synthetic transformation.

After completion of the synthetic sequence, the desired products are cleaved from the beads and subjected to automated mass directed purification, which efficiently removes residual impurities and incomplete products. The platform consistently delivers target molecules in good yields, often surpassing those obtained through conventional solid-phase synthesis. Most importantly, this entire process operates without human intervention. The team can routinely produce hundreds of complexes and multistep molecules in parallel. To date, sequences of up to 30 consecutive reaction steps have been successfully executed on this automated platform. In total, this corresponds to 174 fully automated robotic operations, including reagent additions, protecting-group removals, and bead-washing steps (Fig. 2).

Taken together, the breadth of transformations demonstrated and the ability to seamlessly chain them into extended synthetic sequences represent a genuine expansion of what automated medicinal chemistry can achieve. This is not merely an incremental refinement of existing capabilities; it is the removal of a fundamental boundary that has long constrained automated small-molecule synthesis.

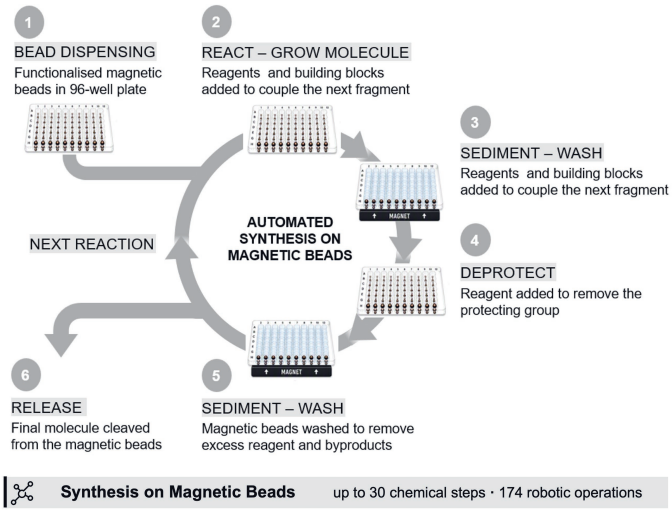

Fig. 2. Magnetic bead enabled automated multistep solid phase synthesis in 96-well plate.

4. Looking Forward

Over the past two decades, GDC has accumulated extensive experience in chemistry automation. The creation of integrated discovery platforms consistently pushes boundaries of what is possible. Today, we can routinely generate hundreds of medicinal chemistry compounds, ranging from relatively simple analogues to complex multistep structures. By synthesising and profiling chemical space at scale, our platforms generate high-quality datasets that fuel predictive models, enable efficient exploration of chemical space and support rapid hypothesis testing across successive DMTA iterations.

Beyond speed, the combination of miniaturisation and chemistry automation is providing a greener medicinal chemistry. By operating on microscale quantities and generating rich multiparametric datasets from minimal starting material, our platforms substantially reduce reagent consumption, solvent usage, and chemical waste. This allows project teams to explore chemical space more efficiently while minimising environmental impact, demonstrating that acceleration and sustainability go hand in hand.

Perhaps even more exciting is the convergence of chemistry automation with the rapid emergence of powerful and agentic artificial intelligence. Opening doors to semi or fully autonomous systems able to optimise a chemical matter towards a given product profile in a closed-loop. Drug discovery workflows in which, design, synthesis, testing, and learning occur with minimal human intervention.[8-12] The MicroCycle active learning loop, already a form of human guided closed-loop optimisation, points directly towards this future.

In this vision, medicinal chemists remain at the centre of innovation, not as operators of routine processes, but as scientists defining strategy, interpreting insights, and tackling the most complex challenges. Self-driving laboratories and AI-enabled discovery are no longer distant concepts; they are becoming a tangible reality, and last two decades of chemistry automation in

GDC have prepared us to help shape this next chapter of medicinal chemistry.

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