Microwave synthesis and knowledge management: A productivity revolution

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Chemistry is critical to drug discovery, especially at the lead optimization phase, but methods for the synthesis of organic compounds have remained essentially unchanged for decades. Lead optimization can take 6 months to 2 years, with a very high manpower requirement, so new ways to improve the efficiency, output and quality in this phase are always needed. One feasible solution is high-throughput microwave-assisted synthesis, in combination with systems to streamline planning and share throughout the organization the enormously valuable knowledge that is created in the process.

Within the next decade, the recent advances in human genomics could swell today's 500 known drug targets to 3,000 to 10,000. Developing drugs for these new targets will be a lengthy and costly process unless the strategies for chemistry development used by the pharmaceutical industry keep pace with the achievements in genomics.

Chemical library synthesis - currently showing a clear tendency to decrease in size and increase in focus - is now a mainstay of the lead optimization process. However, since reaction times with conventional heating are normally very long, compromises have had to be accepted, such as synthesizing many substances in parallel with little scope for variation in the method for the individual library members, and fewer iterative development cycles than are desirable. This may result in lower purities, leading to information from screening which is difficult to interpret, and increasing the risk of a qualitatively poor result.

Multiplying the benefits of speed

Microwave-assisted synthesis is in many ways superior to traditional heating. Reactions are complete in minutes, instead of hours or even days, and result in fewer side reactions. Yields are generally higher than those achievable by traditional means. Microwave heating might solve some 'impossible' chemistry, ie, chemistry not feasible by conventional means. Importantly however, short reaction times with immediate responses give chemists more freedom to explore.

"The reproducibility and scalability of microwave-assisted synthesis reactions are highly compelling reasons to store and re-use the synthesis methods."

Sequential microwave-assisted synthesis is perfect for addressing compound development in the lead optimization phase. At this stage, research chemists explore the possibility of modifying the characteristics of a lead typically by developing a focused library around the chosen backbone structure. Small focused libraries of usually no more than 100 substances can be rapidly developed using sequential microwave-assisted synthesis. The speed of microwave synthesis makes it possible for researchers to rapidly tailor their lead compounds, and sequential processing allows individual, optimized conditions to be applied to each member of the library. The individual monitoring and control of every reaction gives the important benefits of improved reproducibility and scalability of reactions. Moreover, since the investment in time and resources in syntheses is reduced substantially (it is perfectly feasible to synthesize an entire library in one day), chemists can afford to take the risk that a specific avenue of investigation might fail.

The advantages of this strategy over traditional means include faster iterations in method development, rapid optimization of reaction conditions, and, considering the improved reproducibility, even libraries 'on demand'. This results in more iterative cycles (design – synthesis – screening – evaluation) per unit time. The fast feedback enables rapid achievement of a qualitatively better result.

Gaining true productivity

Microwave energy has been used for decades in chemical applications, but mainly applied to digestion and extraction, ie, substance decomposition. The technology was not widely applied to drug discovery until Personal Chemistry introduced the first single-mode microwave reactor designed for organic synthesis, specifically

for lab-scale medicinal chemistry. The domestic microwave oven did not support reproducible results, nor provide the required levels of safety imposed by potentially hazardous organic synthesis reactions, but these problems were solved with the introduction of a specially designed single-mode reactor in 2000.

Microwave-assisted synthesis has since spread rapidly within pharmaceutical R&D. Companies such as Pfizer, GlaxoSmithKline, AstraZeneca, Millennium and Boehringer Ingelheim are well on their way in applying microwave technology as a frontline methodology for library synthesis, making multiple instrument investments within the first years.

Microwave technology can cut the optimization stage from 8 to 2 weeks and accelerated library production from a typical 4-6 weeks down to 3 weeks.

For example, in a recent case at Boehringer Ingelheim, microwave synthesizers from Personal Chemistry were used to optimize, validate, and produce a library of 2-aminoquinolines. The BI combinatorial chemistry group performed a controlled experiment to determine timesavings as well as the return on investment for a microwave synthesis system. The library validation was completed in two days using microwave technology, compared to 37 days with traditional heating technology. Productivity increased by a factor 15 for this specific example, and the return on investment was therefore a mere 5.8 months.

The ongoing development of microwave-based technology is contributing to future generations of microwave systems. Thus, in the future it will be possible to accomplish in minutes parallel synthesis in high-throughput format, yet still with individually controlled reaction conditions. Imagine creating a thousand compounds in 10 minutes, each reaction performed under its ideal conditions to maximize the yield. This would revolutionize combinatorial chemistry.

Great minds think differently

Understanding and utilizing available information is as important as fast reactions. Sharing knowledge not only stimulates chemists to find new avenues of exploration, but also reduces the proportion of repeated work. One chemistry service provider has estimated that some 20-40% of reactions performed in lead optimization have already been done. Repeating work can and should be avoided if research, both successful and failed, is easily recorded and accessible.

Recording and making knowledge available would also enable everybody, not just the specialists, to effectively use the gained knowledge. The level of interaction among team members would probably increase. And even more importantly, if chemists leave the organization, their work continues to contribute to the development process.

New channels for sharing information are required. Although pharmaceutical companies are keen to share information within the organization, they are certainly not interested in doing so via the published literature. The growth of corporate reaction databases and the drive to implement electronic lab journals is evidence of the need to share information selectively.

Compliance and adoption by chemists increases when the solution fits the synthetic chemist's workflow. Figure 1 illus-

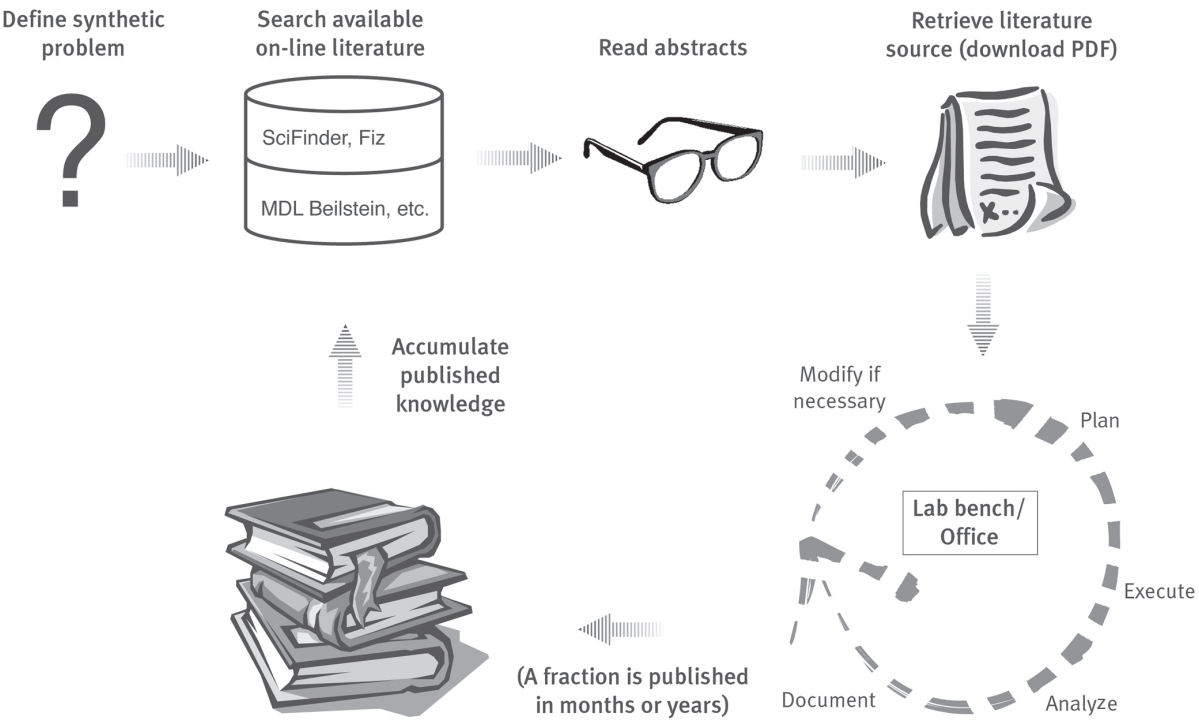

Figure 1. Existing knowledge building is largely based on searching and re-developing methods from published literature. However, the disparity between information gathering and production (indicated by broken arrows) as well as the incomplete collection of information makes the workflow awkward and limits knowledge building.

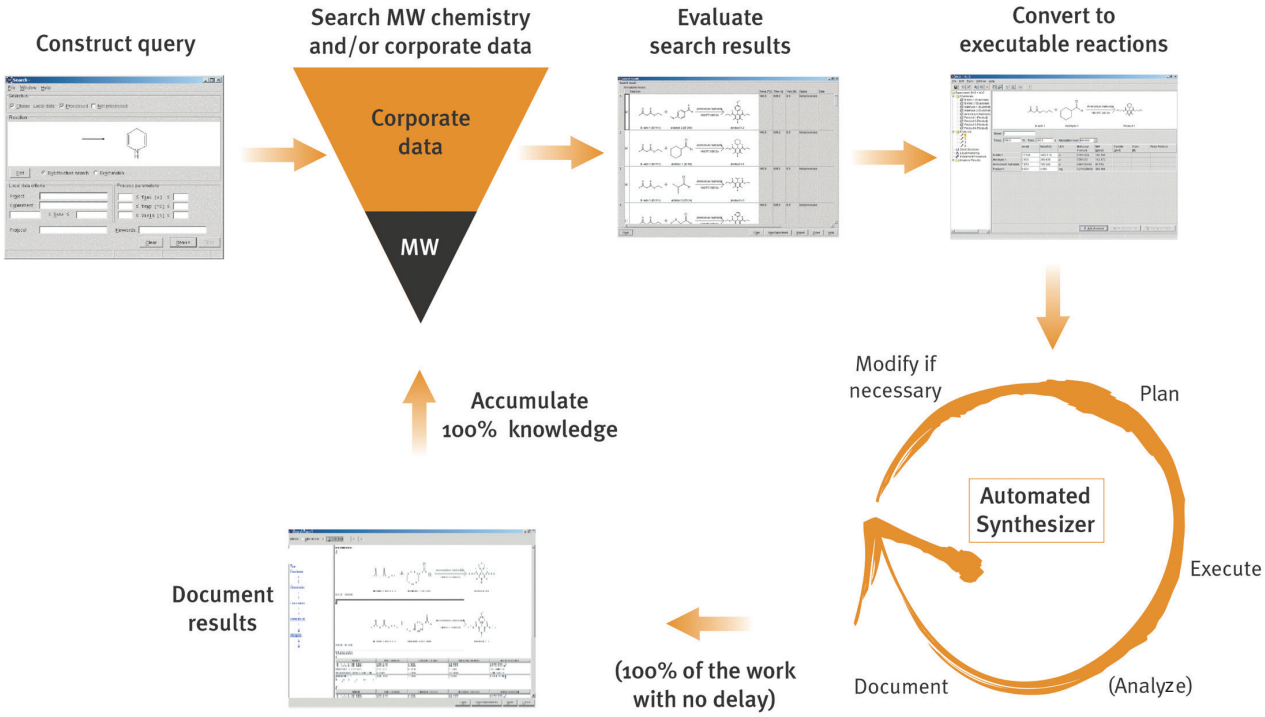

Figure 2. This knowledge building cycle is non-disparate (whole arrows), gathering all the information relevant to the organization's specific lines of enquiry, and integrating knowledge sharing with automated microwave synthesis.

trates the existing chemistry development process of search and 're-development'. Figure 2 illustrates a new working environment where the steps remain the same but the results are cumulative: the time and energy spent at each step contributes to the next step. Moreover, integration of such a database with an automated microwave synthesis system further reduces variability, capitalizes on the reproducibility of microwave synthesis and thereby enhances intelligent discovery.

Microwave synthesis management

The value of keeping comprehensive records of syntheses is arguable if reactions are difficult to reproduce. Traditional chemistry is relatively unpredictable but microwave-assisted synthesis, besides dramatically accelerating reaction rates, improving yields and providing otherwise unattainable transformations, also provides better reproducibility for reactions. Since heating is immediate and volumetric, the temperature is accurately controlled and reactions are more easily repeated.

The reproducibility of reactions that microwave technology supports is the ideal foundation upon which to build a knowledge management system for organic synthesis. A database of reproducible microwave-assisted chemistry provides robust and repeatable starting points for pharmaceutical chemists to build their own novel compounds. The ideal database incorporates verified procedures as well as in-house methods searchable by all corporate sites for global knowledge sharing.

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Administrative work and programming time can be minimized if knowledge management and instruments are connected. Every search result should be immediately executable on a synthesizer. There should be no need for programming a whole library again. Every time a reaction is planned or executed, it should immediately become part of the searchable database.

Therefore, once the chemists have found the reaction they would like to do, more than half of the work is already done. They will only have to substitute their own substrate into the reaction scheme and run the reaction. Their work will increase the chemistry knowledge within the company and work would rarely be done twice.

A coherent approach

It is now generally accepted that microwave-assisted synthesis provides higher yields compared to traditional synthetic methods. Since decisions to proceed with library synthesis are often based on the yields obtained during the library validation phase, basing library design on microwave-assisted synthesis will conceivably result in more 'go' decisions,

accelerating the diversity of compound collections.

By combining microwave-assisted synthesis with verified methods, automation and reaction planning, Coherent Synthesis™ from Personal Chemistry delivers significant advantages for generating focused libraries. In a recent article by Wilson and Roth, the authors show examples where automated sequential microwave synthesis is currently the most appropriate approach for rapidly and reliably generating libraries, with the advantage of allowing for individual, optimized conditions for each reaction. Furthermore, Wilson and Roth point out that microwave-assisted synthesis is compatible with solid-phase synthesis. Furthermore, Ley and Baxendale conclude that microwave-assisted synthesis accelerates the performance of polymer-supported solution-phase synthesis and scavenger resins, which are important and growing technologies for library synthesis.

Personal Chemistry has also developed Emrys™ Liberator specifically to address this approach to library synthesis. Emrys Liberator offers full control and flexibility in focused library design using microwave synthesis, not only fulfilling the needs of medicinal chemistry high-throughput applications, but adding significant advantages over traditional parallel synthesis.

By conferring improved reproducibility of reactions as well as providing the opportunity to set optimal conditions for each library member, Coherent Synthesis has the potential to radically improve output from medicinal chemistry. Emrys Liberator is capable of recording the method and the result of every synthesis, and thus for the first time allowing the generation of libraries 'on demand'.

Being able to instantly share optimized methods among geographically separate research sites is the next step of the Coherent Synthesis vision. The unique proposition of globally sharing reproducible chemistry methods is very likely to change the pace and quality of chemistry development for good.

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FURTHER READING

Wilson NS, Roth GP (2002) **Recent trends in microwave-assisted synthesis.** *Current Opinion in Drug Discovery & Development* **5**:620-629.

Perspective (2002) *Nature Reviews Drug Discovery* **1**:727-730.

Wilson NS, Sarko CR, Roth GP (2002) **Microwave-assisted synthesis of 2-aminoquinolines.** *Tetrahedron Letters* **43**:581-583.

Ley SV, Baxendale IR (2002) **New tools and concepts for modern organic synthesis.** *Nature Reviews Drug Discovery* **1**:573-586.

Creation of new diseases...pushing the boundaries of 'normal'

According to a recent article in the *British Medical Journal*, pharma companies stand accused of sponsoring the creation of female sexual dysfunction in order to build a market, despite controversy surrounding the medicalization of sexual problems.

Key to the alleged creation of this disorder was research published in the *Journal of the American Medical Association* in February 1999, which suggested that 43% of women aged 18 to 59 have female sexual dysfunction, according to seven subjective response criteria. However, leading researchers have raised serious concerns about this figure, describing it as misleading and potentially dangerous.

Ray Moynihan, the author of the BMJ article, claims that the portrayal of sexual difficulties as a dysfunction encourages doctors to prescribe drugs, when attention should be paid to other aspects of the patient's life. But perhaps his greatest concern is the ever-narrowing definition of "normal" which helps turn the complaints of the healthy into the conditions of the sick.

Accusations of disease creation by the pharma industry are not unprecedented of course, but we'd like to know what YOU think of so called lifestyle drugs. Is it irresponsible to turn everyday difficulties into dysfunctions needing drug treatments, or is the question itself simply borne of ignorance? Write to the Editor, Emma Jones, at emma.jones@current-drugs.com.

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