

MICROWAVE-ASSISTED HIGHTHROUGHPUT CHEMISTRY IN LEAD GENERATION AND OPTIMIZATION

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The increasing need for speeding up the entire drug discovery process is one of the reasons driving the recent success of novel technologies that can produce compounds at a very high rate. Microwave (MW)-assisted organic chemistry is a relatively new technology that has been shown to significantly improve productivity in the generation of combinatorial libraries and target molecules [1]. MW high-speed synthesis has attracted a considerable amount of attention in recent years; more than 2000 articles have been published in the area of MW-assisted organic synthesis since the first article on the use of MW heating was reported in literature in 1986. More recently, after the change of the millennium, pharmaceutical and biotechnology companies were increasingly taking on board this technology for highthroughput lead generation, hit validation and lead optimization, but only today we can say that this technique is in some laboratories the first choice of work.

The transition from the use of dangerous domestic MW ovens, that generated data difficult to reproduce due to cold and hot spot problems to very sophisticated professional equipments was very much facilitated by four main companies: Biotage, CEM, Milestone and Anton Paar; all them have large differences between their instruments (often being developed with continuous feedback from researchers in the big pharmaceutical companies), from reaction vessel size and vial option to temperature and reaction monitoring. Some of them allow the chemist to perform up to 50 reactions in parallel; alternatively, single-vessel instruments integrated with an automated arm are available to speed up the serial lead optimization process. Also the optimization of reaction conditions is easily performed since reagents, temperatures, solvents and reaction times can be programmed to run unattended.

All this has helped MW chemistry to gain greater acceptance in all fields of drug discovery and development, from process and analytical areas to organic synthesis and, more recently, scaling-up.

The clue concept is that MW heating dramatically accelerates reaction times when compared to conventional heating in an oil bath. In addition, side reactions are reduced and yields often increased, leading to rapid synthesis of novel and purer compounds. The spectrum of MW-assisted chemistry being explored is becoming larger, touching all fields of solution and solid-phase organic synthesis, including Suzuki, Sonogashira, Stille, Heck, Buchwald, transition-metal-catalyzed reactions and various type of heterocycle synthesis and solvent-free reactions.

The last challenge that producers of MW chemistry equipments are facing is the option to utilize them in scaling up and in the production of large amounts of intermediates or development candidates for preclinical and clinical trials.

Some examples of MW chemistry in the production of hit validation and lead optimization libraries will be discussed in the context of accelerating the drug discovery process.

[1] Kappe, C.O. *Angew. Chem. Int. Ed.* **2004**, *43*, 6250-6284.