

# Automating parallel organic synthesis

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**T**he organic synthesis research and development community faces many challenges entering the new millennium. Increased competitive pressures, rising costs, and rapidly changing markets present major challenges even to industry leaders. However, the age-old goals of increasing productivity while decreasing costs and time to market still prevail. How will chemical research and development evolve to accommodate these expectations in this highly competitive environment? R&D efforts must be linked to increasing market share and profitability. Businesses need to adopt a new management style that integrates technology development with corporate strategic planning and manages R&D for business growth. A key indicator that companies are pursuing this strategy is the rapid development of contract research organizations. Outsourcing allows a company to develop a business plan that provides necessary resources without having to make a long-term investment in those resources. Mergers, collaborations, and joint ventures also provide additional resources within a reasonable time frame without the initial financial and logistical commitments required with an internally developed project.

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Defining new ways to do business has been discussed in many corporate boardrooms around the world. However, defining new ways to do research is paramount in achieving aggressive goals for growth and profitability. Although working smarter and not harder is hackneyed, it speaks volumes about the need to develop tools that will allow a company to efficiently leverage the valuable expertise of its employees.

The drug industry has undergone a dramatic paradigm shift over the last three decades. In the 1970s, companies could profit from drugs shown to be safe and effective, even in the face of multiple competitive products. In the 1980s, with the Food and Drug Administration giving priority to new therapies, companies could achieve profitability only

from drugs that were safe, effective, and novel. Today, with the advent of managed care and cost controls, to be profitable a new drug must be safe, effective, novel, and proven to reduce the overall cost of managing the target disease. With the goal of increasing new drug approvals threefold while concurrently reducing R&D costs and time by 50% over the next five years, the pharmaceutical industry faces a monumental task.

Intelligent automation, integrated workstations, and information management are critical to increasing the efficiency of workflow and information flow. Only with these new tools can pharmaceutical companies achieve their goals of increased productivity with fewer resources. The industry recognizes the value of these areas and is currently relying on integrated, automated systems to help them maintain their competitive edge in the next decade.

Automation has been implemented in many areas of the drug discovery process. From sample preparation through process development, automated high throughput has become the corporate mantra. A major bottleneck in discovery is lead optimization and the critical problem is the slow organic synthesis. Using classical methods at the laboratory bench, the average chemist synthesizes 50–100 compounds per year at a cost of \$5000–7000 per compound. In stark contrast, automated combinatorial chemistry can generate 100,000 compounds per chemist per year at a cost of \$5.00–10.00 per compound. This greater number produced by automated synthesis not only increases efficiency, but also increases the probability of success, because of the tenfold attrition rate with each phase of the drug discovery process. Therefore, the more leads that enter the pipeline, the better the chances of identifying a successful product in the end.

Automation provides two alternatives to the traditional “one-at-a-time” method of organic synthesis. The first, automated lead discovery, generates tens of thousands to millions of compounds in a limited number of steps, based on solid-phase reactions and the “split-and-pool” approach to library synthesis, with mixtures of compounds being synthesized in each reaction vessel. This generates organic molecules in an exponential manner ( $n^x$ , where  $n$  equals the number of building blocks and  $x$  equals the number of steps), which are then tested using automated high-throughput screening to identify lead structures. The second, lead optimization phase of drug

discovery, generates hundreds to a few thousand compounds per library, with one compound being synthesized in each reaction vessel. This parallel or directed approach to synthesis is often used to refine the molecular structure of lead compounds identified during screening. Parallel synthesis is also employed to produce compounds that are designed using structure activity studies.

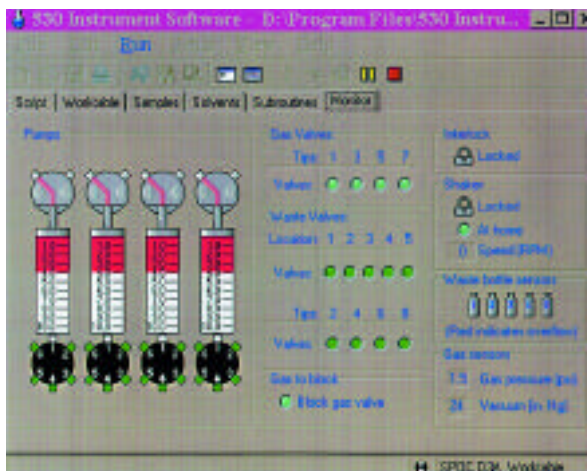
Automated systems must meet the high-throughput demands of the researcher, as well as provide reliability, ease of use, and fail-safe operation. Scientists must feel confident that they can design a synthesis, set up the synthesizer, start the instrument, and leave it unattended until the synthesis is complete. User-friendly, intuitive software is also a critical component of the overall system. Indeed, the computer is often the chemist's primary mode of interaction with the instrument. The Solaris™ 530 organic synthesis system (Figure 1) (PE Biosystems, Foster City, CA) provides fully automated, high-speed parallel synthesis and significantly accelerates the lead optimization process. The system is based on the Genesis robot (Tecan AG, Hombrechtikon, Switzerland). Key features of the instrument include an eight-tip, high-precision liquid-handling system; instrument sensors to monitor inert gas pressure, vacuum, shaker home position, waste level



**Figure 1** Solaris 530 organic synthesizer system, a fully enclosed, floor-standing instrument that provides reliable, automated synthesis with walk-away convenience. Solvent bottles, waste bottles, diluters, valves, and the vacuum pump are housed in the lower enclosure of the system.

detection, and collision detection; a patented, portable, dual-septa synthesis module; and a user-friendly software program (Figure 2). The system is completely enclosed with built-in flow ventilation and a safety interlock to prevent accidental access to the powerful robotic arm and tips while in motion.

The system can accommodate a variety of reagents for creative diverse compounds, solvents, and product racks (Table 1). The portable, chemically inert synthesis module can accommodate 48 glass 10-mL round-



**Figure 2** Chemist-friendly graphical user interface. Six tabs are available to access all key programming functions (script, worktable, samples, solvents, subroutines, and monitor). The Monitor Screen allows the user to view the status of a synthesis in real time.

Table 1

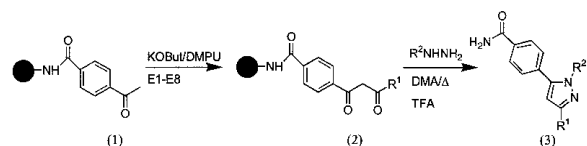
**Reagent and solvent capacity for the Solaris 530 organic synthesis system**

Reagent and solvent positions	Capacity per position
Diversity reagents (144)	12 mL
Common reagents (48)	60 mL
Product vessels (48)	12-mL test tubes or 20-mL scintillation vials or microtiter plates
Solvent bottles (6)	4 L
Segregated waste bottles (5)	5 L

bottom flasks. Each flask holds up to 300 mg of resin for solid-phase synthesis. This capacity yields quantities of compound that are necessary for analysis, purification, screening, and archiving. Inert gas is delivered to all vessels, delivery lines, and the synthesis module for air-sensitive reagents and reactions. The system has a top filtration design and provides on-line cleavage. An off-line incubation workstation capable of heating, cooling, and shaking increases throughput by freeing the system during long incubation periods. The synthesis module is removed from the worktable and placed in the off-line station, while additional synthesis modules can be loaded sequentially onto the worktable to start an additional synthesis.

The organic synthesizer accurately delivers and handles highly reactive solutions widely used in organic syntheses. Examples of reagents that have been used include alkyl- and aryl-Grignards, organolithium compounds (*n*-BuLi, PhLi, LDA), and sodium hexamethyldisilazide (NaHMDS). It has also been shown to deliver fine suspensions of potassium tert-butoxide in *N,N*-dimethyl propylene urea.

An example application using the 530 organic synthesizer is shown in Figure 3. A 0.33-*M* potassium tert-butoxide/*N,N*-dimethyl propylene urea solution (as a fine suspension) was added to the methylketone



**Figure 3** Example of synthesis on the Solaris 530 organic synthesis system.

loaded resin (1). The reaction mixture was shaken over a period of 45 min followed by addition of esters E1–E8, and the reaction was allowed to shake for a period of 48 hr. The reactions were quenched using an aqueous 30% acetic acid solution and each washed successively with water, methanol, dimethyl formamide, and dichloromethane ( $2 \times 3$  mL). HPLC purity was between 60 and 95% for at least 16 out of 20 reactions yielding 1,3-diketones (2). Cyclization was implemented by addition of hydrazines N1–N3 to esters E1–E8 and heating at 90 °C over a period of 24 hr giving the corresponding pyrazoles (3) in 60–95% HPLC purity whose composition was confirmed by mass spectral analysis. Other applications demonstrated on the system have been aryl ether synthesis (Mitsunobu reaction), preparation and addition of organophosphonates (Wittig reaction), and Grignards to aldehyde (nucleophilic additions), as well as C–C bond-forming reactions (C–C Mitsunobu).

The Solaris 530 allows researchers to produce more compounds in a shorter time than traditional methods. From a strategic point of view, this efficiency increases the profitable patent lifetime by reducing time to market. Enhanced throughput also increases the diversity of compounds produced, which in turn increases the number of backup compounds and yields broader patent protection. From an R&D perspective, automated organic synthesis increases the leveraging of valuable intellectual resources—creative organic or medicinal chemists. With automated synthesis systems at their disposal, they can focus their talents on the design of synthetic reactions rather than performing repetitive synthetic procedures at the bench. They can turn over their synthesis protocols for technical staff who can produce the compounds on the automated equipment. Increased throughput in the lead optimization phase of drug discovery provides pharmaceutical companies with a powerful new weapon in their technology arsenal. However, automating organic synthesis will only shift the bottleneck upstream or downstream if complementary technologies are not available. The 530 system is part of a growing family of products being developed to automate all phases of the drug discovery and development process, including target identification and validation, lead discovery and optimization, preclinical testing, clinical development, and manufacturing.

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