Compound libraries tend to grow slowly because chemists have traditionally made compounds one at a time. Into the 1980s, the slow rate of chemical synthesis was not a problem because biological screening methods were also very slow. With biochemical advances and the advent of HTS techniques, however, screening capacity in drug companies increased greatly. Demand for an increase in chemical synthesis followed. The answer was found in **combinatorial chemistry**, or just combichem. Combinatorial chemistry is a method of preparing new molecules using small building blocks in simple, often automated, steps.

An example of a combinatorial library synthesis is shown below. In very simple reactions, one can react an amine (1) with an acid chloride (2) to make a secondary amide (3). Deprotonation followed by alkylation of the nitrogen with an alkyl halide (4) forms a tertiary amide (5). All the reaction building blocks—amine 1, acid chloride 2, and alkyl halide 3—are readily available in a number of different forms. If a chemist had five different amines, five acid chlorides, and five alkyl halides, conceivably 125 different tertiary amides could be made. That is 125 ($5^3$) new molecules from just 15 ($5 \times 3$) building blocks. With ten of each building block, 1,000 new molecules could be made.

The potential value of this type of synthetic approach was immediately recognized. In the early 1990s, combinatorial chemistry grew from being little more than an idea to becoming its own industry. Drug companies created their own combinatorial chemistry teams to prepare molecules. Independent companies created their own libraries to sell or rent to drug companies. Drug discovery seemed poised to enter a new phase of productivity because HTS in tandem with combinatorial chemistry would allow the quick exploration of molecular space for the discovery of new drugs.

Around 20 years later the growth in productivity has yet to materialize as expected. The failure of HTS and combinatorial chemistry is a subject of great debate. Some blame HTS because drug discovery groups relied too heavily on the simple binding data that HTS methods generate. Others blame combinatorial chemistry because the synthetic approach focused upon the wrong types of molecules. Whatever the reason, the major pharmaceutical companies invested deeply into HTS and combinatorial chemistry for questionable returns.

In spite of debates that may surround the recent decisions in major pharma, HTS and combinatorial chemistry remain as very valuable tools to quickly sample the depths of drug space and search for biologically active molecules. The challenge for the pharmaceutical industry is to learn how these tools can be best used to drive the discovery of new drugs.