

# COMBINATORIAL CHEMISTRY: CURRENT APPROACH

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## **ABSTRACT**

Combinatorial chemistry is one of the important new methodologies developed by researchers in the pharmaceutical industry to reduce the time and costs associated with producing effective and competitive new drugs. Through the rapidly evolving technology of combi-chemistry, it is now possible to produce chemical libraries to screen for novel bioactivities.

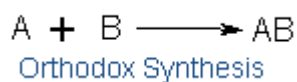
## **INTRODUCTION**

The main objective of combinatorial chemistry is synthesis of arrays of chemical or biological compounds called libraries.(1) These libraries are screened to identify useful components, such as drug candidates. Synthesis and screening are often treated as separate tasks because they require different conditions, instrumentation, and scientific expertise. Synthesis involves the development of new chemical reactions to produce the compounds, while screening aims to identify the biological effect of these compounds, such as strong binding to proteins and other biomolecular targets (2). With this technique, the migration times of the ligand-receptor pair are significantly longer than the unreactive ligands, and can be interrogated by electrospray mass spectrometry. The mass spectrometric method often provides a direct structural identification of the ligand, either by determination of its molecular weight or by collision-induced dissociation experiments. In the latter case, the molecular ion is selected by a primary mass spectrometer and is driven into a region of high-pressure inert gas for fragmentation. The fragment ions are then used to reconstruct the original molecular structure. This direct approach to screening and

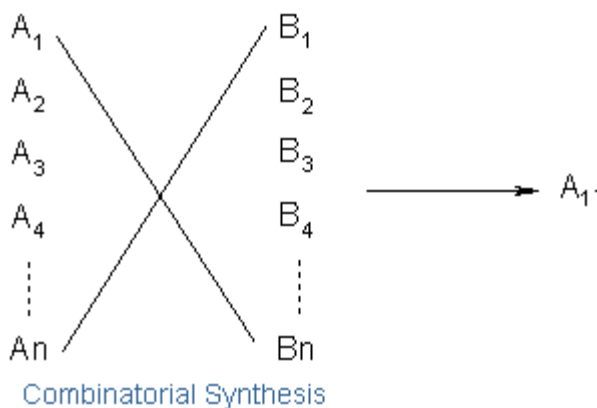
assaying has the advantage that the screening is carried out in solution rather than on a solid support, and it avoids steric problems associated with resin-bound molecules. At present the approach seems limited to libraries of about 1000 compounds because of interference from unbound ligands, and limited by sensitivity issues. New strategies using mass spectrometry may eliminate this limit. (3)(4)

## **PRINCIPLE**

The key of combinatorial chemistry is that a large range of analogues is synthesized using the same reaction conditions, the same reaction vessels. In this way, the chemist can synthesis many hundreds or thousands of compounds in one time instead of preparing only a few by simple methodology.



In contrast to this approach, combinatorial chemistry offers the potential to make every combination of compound A<sub>1</sub> to A<sub>n</sub> with compound B<sub>1</sub> to B<sub>n</sub>.



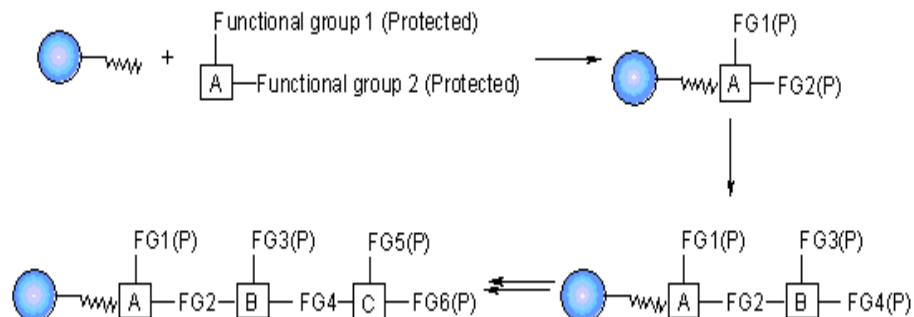
The range of combinatorial techniques is highly diverse, and these products could be made individually in a parallel or in mixtures, using either solution or solid phase techniques. Whatever the technique used the common denominator is that productivity has been amplified beyond the levels that have been routine for the last hundred years.( 5)

## **METHOD OF SYNTHESIS**

## I. COMBINATORIAL SYNTHESIS ON SOLID-PHASE

The use of solid support for organic synthesis relies on three interconnected requirements:

(6)(7)

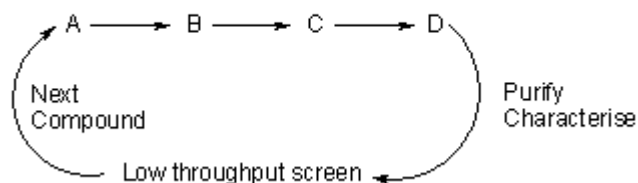


## II.COMBINATORIAL SYNTHESIS IN SOLUTION

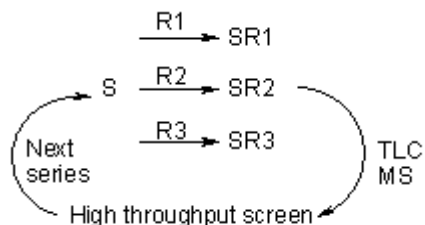
The benefit of preparing libraries on resin beads has been explained as offering advantages in handling, especially where a need to separate excess reagents from the reaction products is attached to the resin. In most of case a simple filtration effects a rapid purification and the product are ready to further synthetic transformation. But it should be remember that using solid phase chemistry brings several disadvantages as well. Clearly the range of chemistry available on solid phase is limited and it is difficult to monitor the progress of reaction when the substrate and product are attached to the solid phase. (8)

## III. PARALLEL SOLUTION PHASE SYNTHESIS (9)

### Orthodox Analogue Synthesis and Screening



### Parallel analogue Synthesis and Screening



## APPLICATION

Combinatorial chemistry is one of the important new methodologies developed by academics and researchers in the pharmaceutical, agrochemical, and biotechnology industries to reduce the time and costs associated with producing effective, marketable, and competitive new drugs. Simply put, scientists use combinatorial chemistry to create large populations of molecules, or libraries that can be screened efficiently *en masse*. By producing larger, more diverse compound libraries, companies increase the probability that they will find novel compounds of significant therapeutic and commercial value. The field represents a convergence of chemistry and biology, made possible by fundamental advances in miniaturization, robotics, and receptor development. And not surprisingly, it has also captured the attention of every major player in the pharmaceutical, biotechnology, and agrochemical arena.

While combinatorial chemistry can be explained simply, its application can take a variety of forms, each requiring a complex interplay of classical organic synthesis techniques, rational drug design strategies, robotics, and scientific information management. This article will provide a basic overview of existing approaches to combinatorial chemistry, and will outline some of the unique information management problems that it generates. Combinatorial chemistry is a promising new field that stands to revolutionize the chemical industry, and

demands completely new scientific information management solutions. Combinatorial chemists will be able to meet their goals if they can find ways to plan libraries quickly, produce libraries that better interrogate biological assays, and learn from past screening results. Using software that can orchestrate the planning, building, screening, and interpretation of synthesized libraries, combinatorial chemistry programs will begin to realize their promise of minimizing the time and cost associated with bringing new molecular entities to market. (10)

## **CONCLUSION**

Combinatorial chemistry is a technology for creating molecules en masse and testing them rapidly for desirable properties-continues to branch out rapidly. One-molecule-at-a-time discovery strategies, many researchers see combinatorial chemistry as a better way to discover new drugs, catalysts, and materials. Compared with conventional one-molecule-at-a-time discovery strategies, many researchers see combinatorial chemistry as a better way to discover new drugs, catalysts, and materials. It is a method for reacting a small number of chemicals to produce simultaneously a very large number of compounds, called libraries, which are screened to identify useful products such as drug candidates and a method in which very large numbers of chemical entities are synthesized by condensing a small number of reagents together in all combinations defined by a small set of reactions.

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