# The significance of combinatorial chemistry in the Drug Discovery

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**ABSTRACT**

The 'Combinatorial chemistry' means the systemic & repetitive covalent connection for benefit of different building blocks of varying array of divergent molecular entities. Combinatorial chemistry is redefining the way pharmaceuticals and other high performance the chemicals and materials are discovered and developed. Using a novel technique called combinatorial chemistry; we can create several potential molecules that could concurrently produce a huge number of libraries of compounds. In CADD, combinatorial chemistry is particularly prevalent ('Computer aided drug design') which will be carried out networked using online-based technologies based on Mol inspiration. Traditionally, chemists have created one compound at a time. It provides faster, cheap and more comprehensive exploitation of new drug targets. Nowadays these techniques are now commonly used in tandem in any given discovery project.

## I INTRODUCTION

Combinatorial chemistry is systematic and recurring covalent bonding of various chemical entities. The lead discovery and optimization process in the pharmaceutical business has been merged with combinatorial chem. coupled with HTS and computational approaches. A huge number of various but frequently structurally related compounds or materials are rapidly synthesized or computer simulated in combinatorial chemistry. In a 'combinatorial preparations', the various number of compounds produced rises aggressively as more chemical

reactions are performed. 2n molecules can be created in n chemical steps during a binary light-directed synthesis. The 'Combinatorial chemistry' is frequently used in 'CADD' and can be performed online using web-based applications like Particle. 'Basic combinatorial chemistry' prototype was first disclosed by Eddington in 1927. This is a technique for regularly combining vast numbers of small molecule chemical building blocks together to make all possible combinations according to a specified chemical reaction arrangement. This provides for the rapid production of ***libraries*** of hundreds, or thousands, of diverse molecules that would have previously taken chemists years to outright, synthesizing them one-at-time. The more compounds in a library, the greater the chance that one will be found to match the active site on a biological target. Eventually, this should lead to decrease time for drug discovery and more cost effective use of pharmaceutical discovery resources.

Preparations of molecules in a combinatorial way can quickly lead to enormous numbers of particles. Researchers frequently develop a "virtual library," a computer tool, to pick-up the enormous number of structural options. Listing all potential 'pharmacophore' structures with all available data reactants. These "virtual" compounds can number in the thousands to the millions in such a library. Based on a variety of factors, the investigator will choose a portion of the "virtual library" for actual synthesis. One of the key new fields in chemistry is combinatorial chemistry created by experts in the pharmaceutical sector to speed up the process. The expenses related to creating innovative drugs that are both effective and affordable. By quickening chemical synthesis, this approach is having a significant impact on all fields particularly on the discovery of new drugs. This powerful new technology has started to help pharmaceutical companies to search new drug candidates quickly, save more money in preclinical development costs and finally change their fundamental approach to 'drug discovery'.

**Historical Development**

Key milestones of Drug Discovery

| Year | Class | Contributors | Development. |
|---|---|---|---|
| 1963 | P | Merrifield | Synthesis- 'Solid-phase peptide' |
| 1970 | SM | Leznoff | Synthesis- Early non-peptide solid-phase |
| 1984 | P | Geysen | Parallel synthesis- Multipins |
| 1985 | P | Houghten | 'Teabags' |
| 1988 | P | Furka | Mix-and-split Preparation |
| 1991 | P | Fodor | parallel synthesis (Light-directed spatially addressable) |
| | P | Houghten | Mixtures Screening |
| | P | Lam | one bead, one peptide (On-bead screening) |
| 1992 | P | Houghten | Positional scanning |
| | SM | Ellman | synthesis of Benzodiazepines (Solid-phase) |
| 1993 | SM | De Witt | Diversomers (parallel solid-phase synthesis on resin) |
| 1994 | SM | Smith | 'Indexed libraries' |
| 1995 | P | Deprez | 'Orthogonal libraries' |
| 1996 | P | Ni | 'Secondary amine' tags for encoding |
| | SM | Curran | For reagents and Substrates (Fluoroscans tags) |
| | SM | Cheng, Boger | Preparations of mixtures by solution chemistry |
| 1997 | SM | Lipinski | Design: developability |
| 1999 | SM | Ley | Multistep solution (preparation by supported reagents) |

## 1. PRINCIPLE OF COMBINATORIAL CHEMISTRY

The fundamental idea for the investigations is to produce a vast number of compounds, followed by extraction additional molecules from them. This is a technique by which separate molecules with high structural dimensions can be created in a less time and further for pharmacological study. Investigator can gather numerous numbers of compounds; quickly utilize a straight forward process and the idea of 'combinatorial chemistry' is extremely important in material science & drug discovery.

Basic idea of this study includes,

• At one time formation of many compounds
• Effective substance by high throughput-screening

**2. COMBINATORIAL CHEMISTRY APPROACH**

Combinatorial chemistry covers many ideas for the rapid synthesis of large, organized collections of compounds called libraries. After collection it is screened for the biological activity. At last, the active compound is identified and mass-produced as a single compound. So the combinatorial chemistry approach has two stages:

1. Making a 'combinatorial library'
2. Searching the 'active compound'

Screening mixtures for 'biological activity' is very tough. However in the past, chemists are successful in preparation of one compound at once.

For example compound A will reacted with compound B to give product AB, which will have been isolated after reaction work up and purification through crystallization, distillation or chromatography. In contrast to conventional approach, It gives the potential to make every combination of compound $A_1$ to $A_n$ with compound $B_1$ to $B_n$

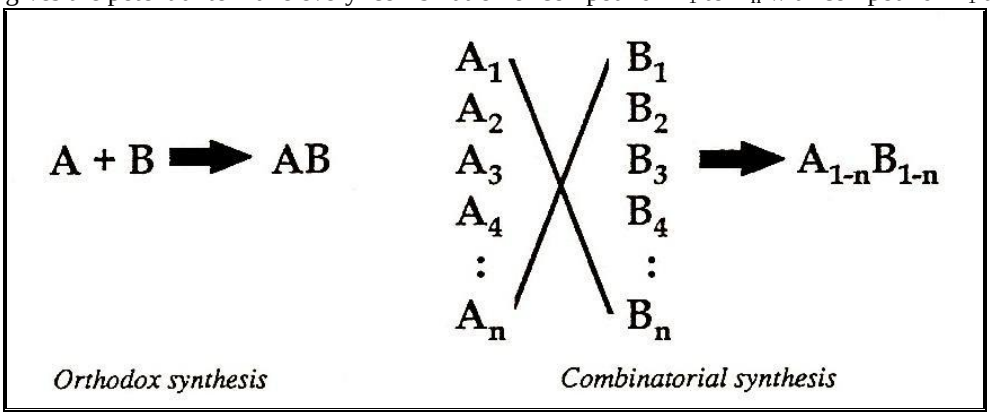


**Fig. 1: Orthodox synthesis Vs Combinatorial synthesis.**

The scope of combined technologies is very varying and these products can be manufactured individually in parallel or in mixtures using solution or solid phase technologies. It was found that productivity levels have been greatly increased beyond what has been typical in the last hundred years. Combinatorial chemistry is a technology that is used to create molecules and test them quickly for desirable properties. This field of research is expanding rapidly, and new applications are being developed all the time. Many researchers see combinatorial chemistry as a better way to discover new drugs, catalysts and materials than using one-molecule-at-a-time discovery strategies. The development of new processes for the generation of structurally related compounds (libraries) with the introduction of 'combinatorial approaches' has revitalized random screening as a paradigm for drug discovery and has raised enormous excitement about the possibility of finding new and valuable drugs in short timeframes

**3. TYPES OF COMBINATORIAL LIBRARIES**

- Scaffold-based Libraries: Core-structure, that is common to all compounds of the library.
  Ex: Amino acid and Amino Benzophenone.
- Backbone-based Libraries
  Ex: Nucleic acid, Carbohydrate.
- Two techniques to generate libraries are Random libraries, Focused libraries.

**6. COMBINATORIAL CHEMISTRY-METHODS**

**6.1 Solid Phase Technique**

The reactants is attached to a polymeric surface and developed at the same time attached. Finally the product is released at the end of the preparation.

**6.1.1 Requirements**

• For solid support resin beads are used.
• The anchor or linker.
• A 'bond linking' the substrate to the linker.
• Remain stable to the reaction conditions used in the synthesis
• A indicate cleaving the product from the linker at the end.
• Protecting groups for 'functional groups' which are not involved in the synthesis.

**6.1.2 Solid phase tool**

• Beads must remain stable & it should swell in the solvent used.

• Most reactions occur in the interior of the bead.

**6.1.3 Anchor or linker**

A molecular moiety which is covalently attached to the solid support, and contains a reactive functional group

• Enable linking of the first reactant

• The link must be easily cleaved to release the final compound & remain stable to the reaction conditions in the preparation

• Many linkers are available depending on the functional group to be attached & the desired 'functional group' on the product

• Resins are mention to define the linker

Eg: Merrifield, Wang, and Rink

Solid phase preparations (protecting groups)

The protecting groups used in solid phase synthesis.

**Amines**

Boc (tertary-butoxycarbonyl)

Fmoc (9-fluorenylmetoxy carbonyl)

Tmsec (2 [trimethylsilyl] ethoxycarbonyl)

**Carboxylic acids**

• Tertiary Butyl ester (t-butyl ester)

• Fmester (9-fluronyl methyl ester)

• Tmseester (2 [trimethylsilyl] ethyl)

**6.1.4 Advantages**

• The specific reactant can be bound to specific beads

• The bead can be mixed and reacted in the same reaction vessel

• The product formed is distinctive for each bead and physically distinct

• The more amount of reagent can be used to drive reactions for completion.

• The more amount of reagent and by products are easily removed

• 'Reaction intermediates' do not need to be isolated & purified and are attached to bead.

• The Individual bead can be separated to isolate products

• The Polymeric support can be regenerated and re-used after cleaving the product

• Automation is successful.

**6.2 Parallel Synthesis**

**6.2.1 Parallel Synthetic method**

• To use a standard synthetic rout and to produce a range of analogues, with a different analogue in each reaction vessel, tube or well

• The identity of each structure is well-known

• Useful for producing a range of analogues for drug optimization and Structure Activity Relationship

**6.2.2 Tea bag (Houghton's) Method**

• Every tea bag contain bead which is labeled.

• Separate reaction is carried out on each tea bag

• Combination of tea bags for work up procedure and for common reaction.

• Within each teabag a single product is prepared.

• In different teabags many products are formed

• Economy of effort (combining tea bags for workups)

• For many labs it is cheap and accessible.

• Manual procedure and is not suitable for producing large quantities of different products.

**6.2.3 Automated parallel synthesis**

• 'Automated preparations' are available with 42, 96 or 144 reaction vessels or wells.

• 'For solid phase support' use beads or pins

• Automatically reactions and work ups are carried out

• Same synthetic route used for each vessel, but different reagents.

• Every vessel different products are formed.

**6.3 Mixed Combinatorial Preparations**

• By using a standard synthetic route, to produce a large variety of different counterpart where each reaction vessel or tube contains a mixture of products.

• The identities of the structures, in each vessel are not known with certainty.

• Useful for searching novel lead compound.

• Helpful of preparing large number of compounds quickly, each mixture is tested for activity as the mixture.
• Inactive mixtures are stored in combinatorial libraries.
• Active component can be identified by studying mixtures.

**6.3.1 The Mix and Split Method**

Ex: Preparations of five amino acids are used to prepare possible dipeptide.
The method involves 25 separate syntheses.

**6.4 Solution phase synthesis**

This assay usually in the 96-well plate format, it is used in mass screening for most drug discovery programs. There are various solution phase assays available.

**6.4.1 Combination of on Bead and Solution Phase Screening Assay**

It may be advantageous to combine solution phase assays with on bead assays to screen a specific target. Positive beads isolated by this approach are more likely to be true positives Eg. The compound beads are partitioned in to 1000 beads per well and a portion of the compound on each bead is released into the solution for biological testing.

**6.5.1 The Multipin Method:** In parallel procedures an array of different substances are simultaneously prepared. Geysen et al and his colleagues published the first example of parallel synthesis. They have a series of peptides epitopes in an apparatus developed for this purpose. The multipin apparatus had a block of wells serving as reaction vessels and cover plate with mounted polyethylene rods fitting into well.

**6.5.2 One bead one compound technique**: In this method for each possible structure a specific quantity of beads is allocated in the library; those beads contain only molecules of the given library member. The beads may be tagged in various ways to help identify the prepared compound. The advantage of the one bead one compound strategy is the simplicity of analysis & screening.

**6.5.3 Iterative deconvolution**: It is used when combinatorial chemistry was started. Each group has beads bearing a variety of compounds, but a given structure only appears in one of the groups.

**6.5.4 Subtractive deconvolution:** This is the strategy similar to iterative deconvolution but uses negative logic, namely, leave out a functional group, & if activity is absent, the functional group that is missing must beneeded for activity. This is particularly useful for 'QSAR-type studies' in which, a cl group is placed at several positions on a phenyl ring.

**6.5.5 Detection by Bogus-coin:** This starts with generating & screening the entire library as a single mixture. If activity is found, the building blocks are divided into 3 groups (alpha, beta, & gamma) then sub libraries are prepared.

**6.5.6 Orthogonal pooling:** It means perpendicular/uncorrelated. In this type of pooling, we distribute the functional groups to be considered into sets of libraries like A, B, C etc., which can contain mixtures of the same compounds. However, the functional groups are distributed such that any subset in A, B shares only one functional group.

**7. IMPORTANCE OF COMBINATORIAL CHEMISTRY IN DRUG DISCOVERY**

Drug discovery process is very nexus.it involves four key stages; the first is the discovery and definition of a *biological target*. This is a protein with involvement in a disease process. The success of the Human Genome Project is to provide a blueprint of the human genome, in combination with the complementary approach of proteomics, is the extraordinary rate of innovation and considerate of new goals.

This is set to have a deep effect on drug discovery in the new era. When a relevant target has been known, assays are developed to detect molecules that bind to the target and modify its performance in the chosen manner.

The process now enters the *lead generation stage*. Here, the goal is to identify a lead compound whose properties make it a suitable applicant for more full exploration. In most cases this involves a high-throughput screening exercise, where enormous numbers of compounds are screened beside the target in the assay developed previously. When the greater the number of suitable compounds obtainable for screening then the greater the chance of success. The invention of lead discovery libraries was an early driver for combinatorial chemistry and continues to be an important application. Libraries for this purpose are typically of significant size, from a few thousand to tens/ hundreds of thousands of compounds and may occur in a number of formats that match the broadcast protocols in use. Libraries on solid supports need alternative screening policies, which may be particularly suited to certain specific target classes then are unlikely to be as generally applicable as solution assays.

When information of the three-dimensional structure of a protein is known, either through x-ray diffraction studies or through homology demonstrating, de novo design of a library ofcompounds is a possibility. Computer modeling of the interactions between candidate small molecules and the known active site of the protein can provide a startingpoint for library design. Such an approach will often take place in similar with highthroughput screening exercises.

Once a suitable lead is identified, the compound enters the third stage of the process,

optimization. The goal here is to modify the lead structure such that a number of criteria for progression into the final, *development*, *stage* are satisfied. Important criteria, the actual values of which will be set on a case-by-case basis, include high potency against the target as well as selectivity against related targets.

Combinatorial chemistry at this stage is to deliver sets of compounds with which to originate an understanding of the contribution of structural elements of the molecule toward its binding to the protein target, so that 'structure–activity relationship' can be established. Lead optimization libraries typically consist of hundreds or a few thousand compounds at maximum. As the 'iterative cycles' of library design, synthesis, and screening development and more is known about SAR, the library size might fall to a handful of compounds concentrated on fine-tuning some aspect of the overall profile. The elevated product will enter the final, although most lengthy and costly stage, that of development into a marketable drug, including optimization of synthetic paths for production-scale synthesis, strict trials in patients to verify clinical efficacy and safety, regulatory approval, and marketing; It is only once sales have begun that the considerable research and development costs can start to be improved, and this is possible only until the patent life of the compound finishes.

**7.1 Advantages**

1. Combinatorial chemistry to generate large populations of molecules that can be screened well.
2. Companies increase the possibility that they will find original compounds of significant therapeutic and marketable value.
3. A incentive for 'robot-controlled' and immobilization strategies that allow high-throughput and multiple parallel approaches to drug discovery.
4. Using combinatorial techniques compounds that cannot be produced using traditional methods of medicinal chemistry can be manufactured.
5. The cost of combinatorial chemistry library generation and analysis of said library is very large, but when considered on a per compound basis the price is significantly lesser when compared to the cost of individual synthesis.
6. More chances to produce lead compounds.
7. 'Combinatorial chemistry' speeds up drug discovery.

**8. CHALLENGES IN COMBINATORIAL CHEMISTRY**

- To design and matching a target with the diversity-producing chemical scheme-including the choice to produce individually or as a mixture.
- To Comfort that the desired range of compounds is manufactured.
- To Judge which compound is active within mixtures that test "active"-deconvolution of the mixture.
- Manufacturing a strong scheme for fastening the synthesized compound in the case of solid-phase preparation.
- Automation of certain synthesis and screening schemes.
- To manage the data pertaining to the synthesis and assays.

The total platform, including the select of compounds, chemical reactions, deconvolution scheme, assay method, compound identification, data handling, automation, and quality control needs to work together harmoniously to fulfill the original purpose, namely-to improve the degree of innovation and productivity in drug discovery or lead optimization.

**9. FUTURE SCOPE OF 'COMBINATORIAL CHEMISTRY'**

In the past decade has seen an explosion in the exploration and adoption of combinatorial techniques. It is difficult to identify any other topic in chemistry that has ever caught the imagination of chemists with such passion. For pharmaceutical chemists at least the reason for this change is not hard to understand. 20 years ago the market for pharmaceuticals was growing at around ten 10 percent per annum but more recently the rate of the market growth as drop. At the same time, cost controls on pharmaceutical research have forced the investigation of methods that offer higher productivity at lower expenses. The belief that combinatorial chemistry will allow the productive and cost-efficient generation of both compounds and drug molecules has powered huge investment in this area.

**10. CONCLUSION**

- Combinatorial chemistry is a technology for creating molecules masse and testing them rapidly for desirable properties-continues to branch out rapidly.
- Many researchers see combinatorial chemistry as a better way to discover new drugs, catalysts, and materials.
- Many researchers conclude that combinatorial chemistry as a better way to discover new drugs, catalysts, and materials.

- 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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