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# A Review on Combinatorial Chemistry

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## Review Article

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**ABSTRACT**

Present review article is the study on the combinatorial chemistry. This study is important when introducing drug molecule in to clinical therapy. Combinatorial chemistry means the systemic and repetitive covalent connection of different molecular entities i.e., with different building blocks. We are studying the principle, design of combinatorial chemistry. We used different approaches for *creating chemical libraries and identification of active ingredients with different types and their advantages and disadvantages. Further detailed study deals with* methods of combinatorial chemistry in which methods are responsible for formation of new molecule with the huge application of combinatorial chemistry with systemic and repetitive connection by chemical bonding. We also studied the biological activity of newly synthesized molecule against their targets.

## INTRODUCTION

### Drug Discovery

The fields of medicine include medicinal chemistry, pharmacology, pharmaceutical biotechnology by which drug entities are discovered. Many decants drugs were discovered for identifying the active ingredient from traditional entities discovery. Recently synthesized small entities, natural formulated products or extracts were screened in intact cells or whole materials to identify substances which are desirable for therapeutic action. Sequences of the human genome which are allowed to synthesize large amount of purified proteins and rapid cloning it has shown the common practice to use of high throughput screening that leads to large chemical molecule against biological events i.e., targets to be disease modifying known as reverse pharmacology. After that these are then tested in cells and then in animals for potency. Because of understanding shape of biological molecule at atomic level by researchers they are able to design drug candidate [1].

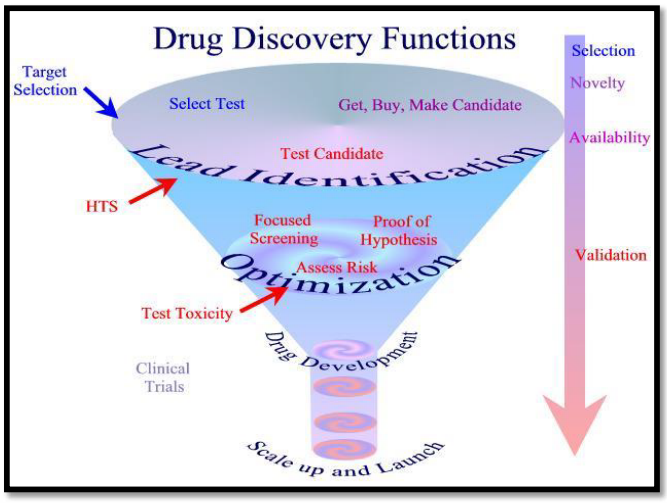


**Figure 1.** Drug Discovery functions [2].

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**Combinatorial Chemistry**

Combinatorial chemistry is defined as the systemic and repetitive covalent connection of asset of different building blocks of varying array of diverse molecular entities.

Combinatorial chemistry coupled to HTS and computational methods and has been integrated into lead discovery **(Figures 1 and 2)** and optimization process throughput the pharma industry [3].

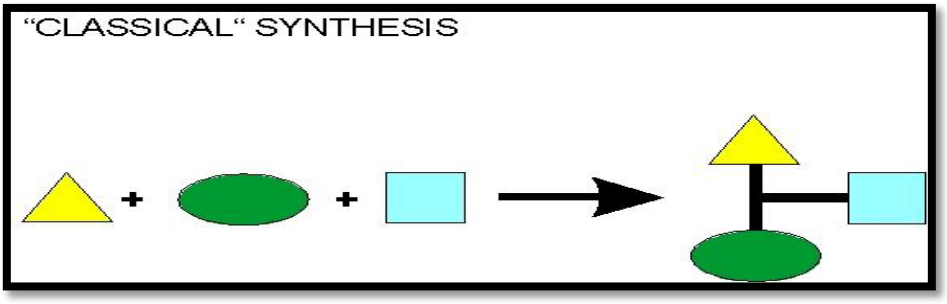


**Figure 2.** Classical synthesis [4].

**Principle of Combinatorial Chemistry**

The basic principle of these studies is to prepare very large number of compounds and then identify more components from these compounds. It is a technique by which distinct molecule which is structurally large may be synthesized in a short time and submitted for pharmacological study. Researchers can synthesize many numbers of compounds in a short time by using simple methodology.

**Basic Concept of Combinatorial Chemistry**

The concept of combinatorial chemistry is very important in material science and drug discovery.

Basic idea of this study:

- Formation of number of compounds in one time **(Figure 3)**.
- High throughput-screening which gives effective substances **(Figure 4)**.

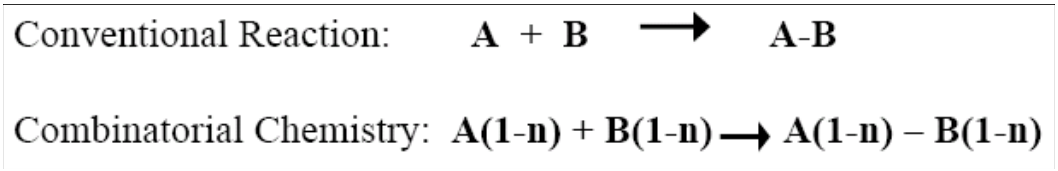


**Figure 3.** Formation of number of compounds at a time.

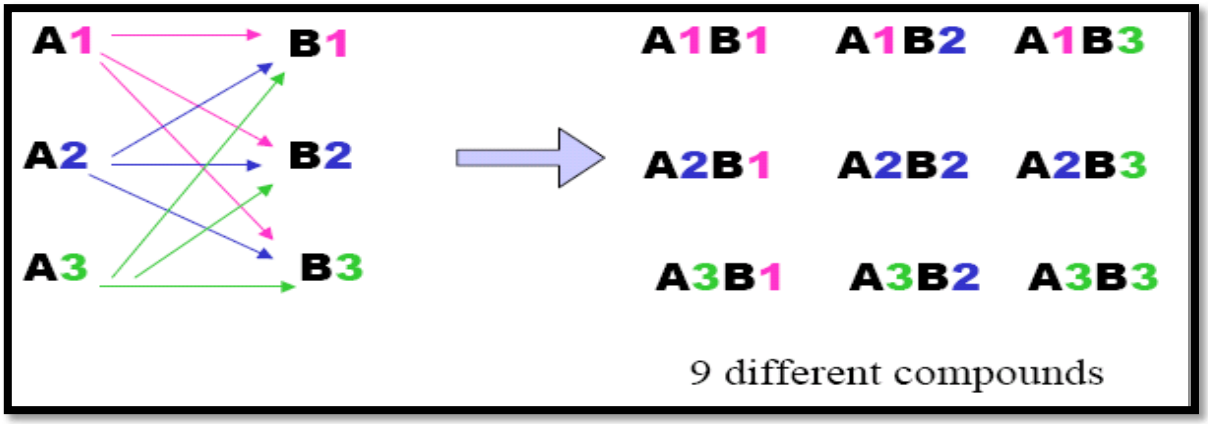


**Figure 4.** High throughput-screening which gives effective substances.

Combinatorial chemistry differs from traditional synthesis. In that, it involves the simultaneous reaction of one set of compounds with a second set of compounds to produce a set of products known as combinatorial library. Formation of large number of compounds which are structurally different is very important to increase the chances of finding 'HIT' and to increase the diversity of compounds and number produced in each reaction [5].

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**Design of Combinatorial Chemistry**

One of the two general strategies may be followed while designing a combinatorial synthesis **(Figure 5)**.

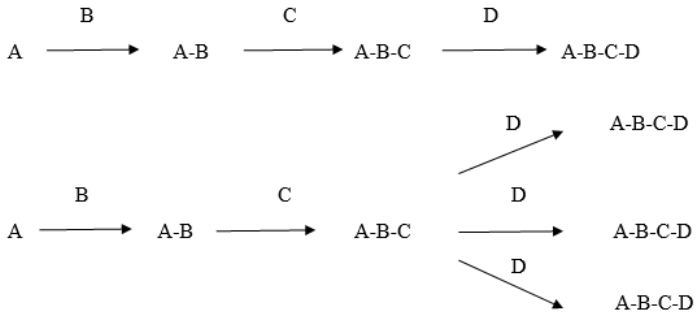


**Figure 5.** Design of Combinatorial Chemistry.

- A sequential attachment of building blocks.
- The non-sequential attachment of building blocks using B as a template.

In the first case, the building blocks are successively added to the preceding structure so that it can grow in only one direction.

## COMBINATORIAL APPROACH

*Combinatorial approach has two phases -*

- *Creating chemical libraries.*
- *Identification of active ingredients.*

***Creating Chemical Libraries***

Compound library or chemical library is a collection of chemicals storage regularly used in industrial manufacturing and high-throughput screening. These chemical libraries are simple in terms of a series of excessively stored chemicals. Each stored chemical has associated information such as the chemical structure, physiochemical characteristics, purity, quantity of the compound **(Figure 6).**

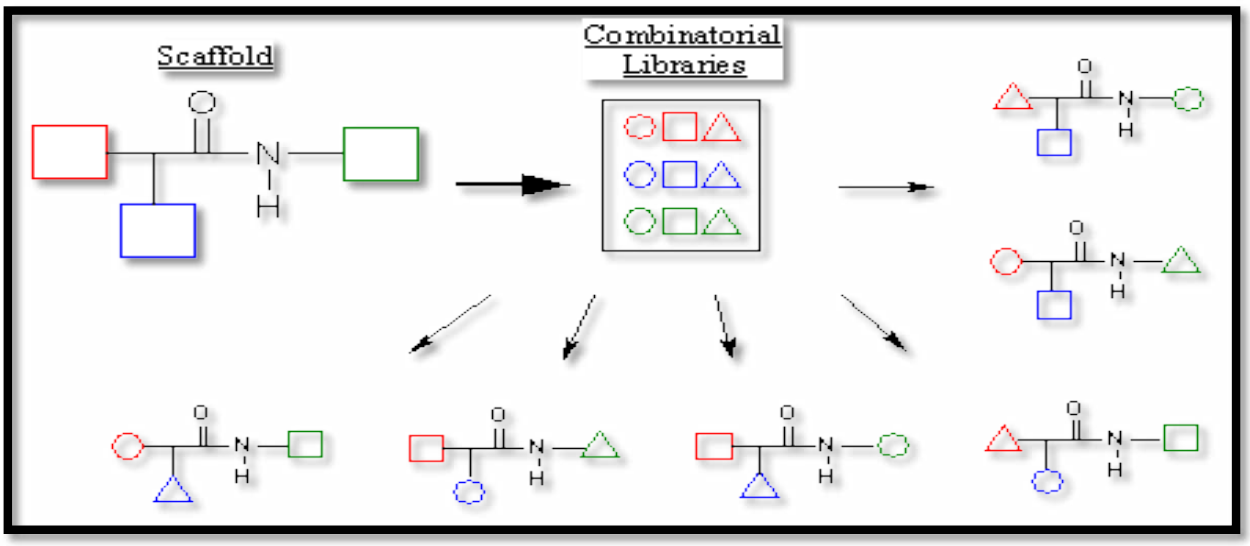


**Figure 6.** Chemical libraries.

**Types of Combinatorial Library**

***Scaffold-based Libraries***

Definition: Core-structure, which is common to all compounds of the library.

Several single building blocks can consist of Scaffold.

Example- Amino acid and Amino Benzophenone.

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***Backbone-based Libraries***

Example- Nucleic acid and Carbohydrate.

Two approaches to generate libraries are Random libraries and Focused libraries.

**Function of Combinatorial Library**

***Optimization and Identification***

Example- In the process of new drug discovery [6]. Combinatorial chemistry has two basic techniques for creating chemical libraries: Split and mix synthesis method and Parallel synthesis method.

***Split and Mix Synthesis Method***

In this method, ingredients are assembled on the surface of the beads or micro particles. In each step, beads from last steps are partitioned into new building block and several groups are added. This leads to the formation of new groups, the different groups of beads are recombined and separated once again. Process is continuous with next building block is added until the desired library has been assembled (Figure 7).

**Advantages**

- Method of having choice for large libraries.
- Less reaction vessels required.

**Disadvantages**

- Less amounts of the synthesized compounds available.
- Three-fold amount of resin beads necessary.

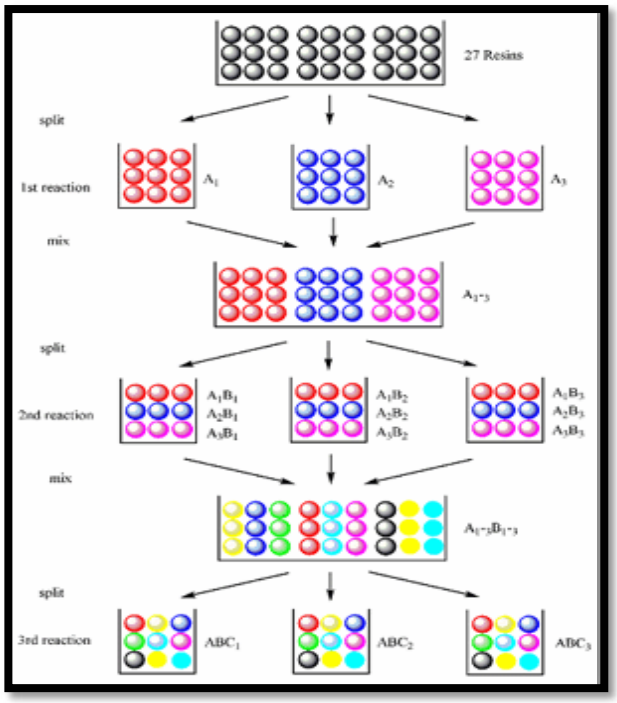


**Figure 7.** Split and mix synthesis [6].

**Parallel synthesis:** In separate vessels, different compounds are synthesized (without re-mixing). This is not like a split synthesis because it requires a solid support. It can be done without solid support or in a solution. A 96 well micro titer plate is commonly used format for parallel synthesis **(Figure 8)**.

Methods of parallel synthesis include Houghton's tea bag procedure and Automated parallel synthesis.

Advantages

- Biological evaluation is easy
- Each compound is substantially pure in its location
- Defined location provides the structure of a certain compound

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Disadvantages

- Applicable only for particular libraries

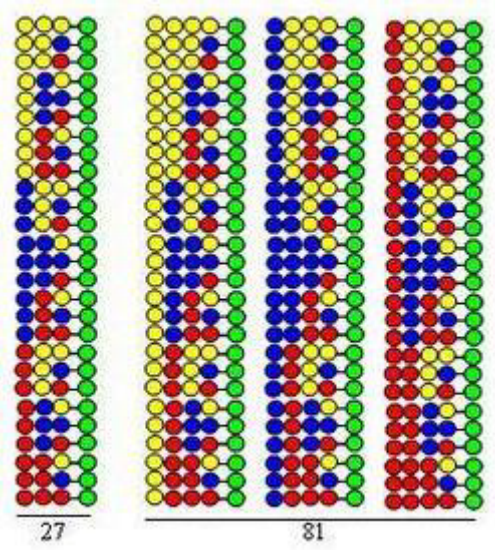


**Figure 8.** Parallel synthesis [6].

### Identification of Active Ingredient

Major challenge in developing library of compounds is screening the library for the activity of the chemical species responsible. The goal of producing molecular libraries is to discover compounds that have some desired properties to serve as a drug.

- Analytical techniques
- DNA based encoding
- Mass encoding
- Peptide tag
- Hard tag
- Radio frequency encoding [7].

## METHODS OF COMBINATORIAL CHEMISTRY

### Solid Phase Synthesis

There are various types of linkers which are used for starting compound and are attached to an insoluble resin bead **(Figure 9)**. Polystyrene is 1-2% divinyl benzene, most commonly used in combinatorial chemistry. It's particularly useful for multistep reactions, intermediates resulting in each step can be isolated quickly by this method. Another advantage is that removal of unreacted reagents is possible, excess molecules can be used for the completion of the reaction [5].

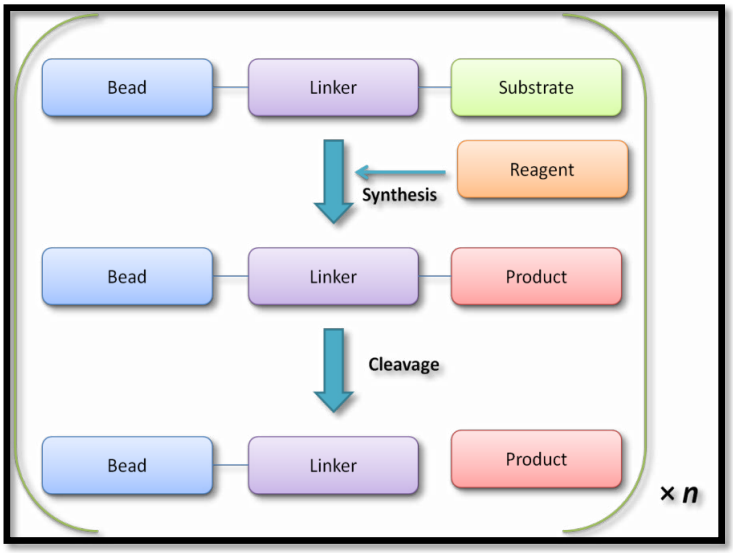


**Figure 9.** Solid phase synthesis [8].

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Solid phase synthesis resins: Tenta gel resin, Polyamide resin, Cross-linked polystyrene.

Linkers for solid phase synthesis: Alcohol linkers, Traceless linkers, Carboxylic acid linkers, Amide linkers, Carboxamide linkers.

**Solution Phase Synthesis**

There are different multiple techniques available for this synthesis and because of that its use is increasing. Isolation of the product is the biggest challenge in this synthesis. Ion exchange resins are currently in use. Also, several new techniques have been introduced to make the extraction process easier. These methods remove byproducts and therefore eliminate the need for an aqueous work up. It eases extraction of the final product. Fluorous phase-chemistry is another method in solution phase synthesis [5].

Advantages

- Purification is easy.
- Handling of material is easy and can be automated.

Disadvantages

- Quantities produced can be very low for very large libraries (maybe as low as 10s of nanomoles).
- Solution phase methods don't always work when compared to the solid phase.
- Characterization of intermediates is difficult as we can't tell if our reaction has worked or not.
- We can't surely detect which compound is attached to any one bead. ("deconvolutio") [9].

**Parallel Synthesis**

It involves multiple reactions, at once instead of in series, each in a separate vessel. Parallel synthesis is possible when it advances in automation. This synthesis is allowed the production of huge no. of individual entities but split and pool methods are capable of huge numbers in very less time and this is better for the drug discovery in earlier stages **(Figure 10)** [5]. One of the subtypes of this method is automated parallel synthesis **(Figure 11).**

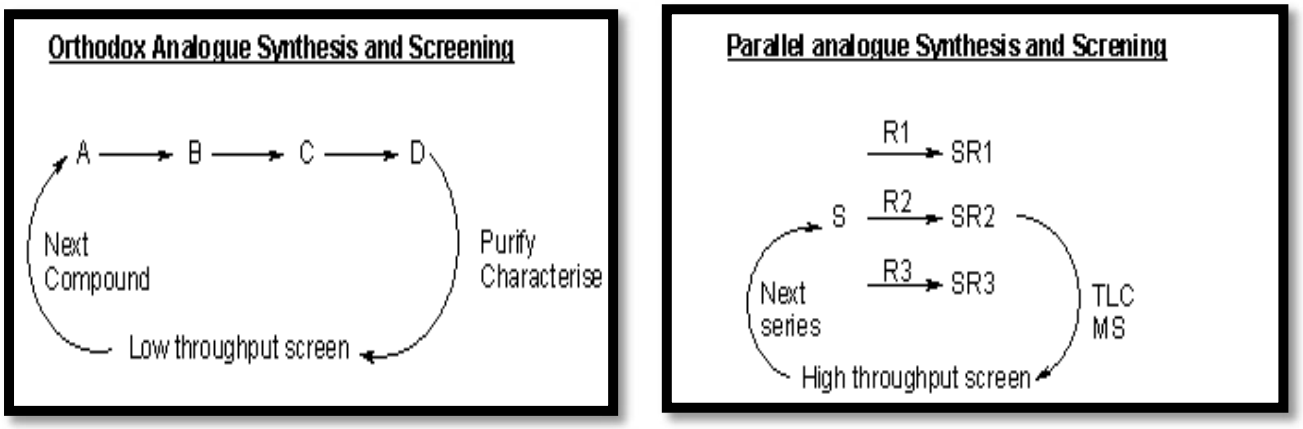


**Figure 10.** Parallel synthesis [10].

*Advantages*

- *Easy to identify active hit as its position (X, Y coordinate) in the array encodes the reagents and thus structure of the product.*
- *New equipment, such as 'personal synthesizers' and 'multi vial apparatus,' allows parallel synthesis of many compounds simply and quickly by one chemist.*
- *Robotized technology.*

*Disadvantages*

- *Maximum impurities can occur unless the reactions are very clean.*
- *Most useful for one to three step reactions only.*
- *Can only be used for making smaller (more focused) libraries.*

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**Figure 11.** Automated synthesizers [9].

## APPLICATIONS OF COMBINATORIAL CHEMISTRY

Drug discovery is a competitive discipline that requires constant innovation and refinement as a combination of market, patient, and regulatory concerns. It is required that companies balance their novel, clinically invalidated molecular targets with validated targets (KO, ASO, siRNA) because the attrition rate for novel targets is substantial [11].

### Combinatorial Lead Optimization of Histamine $H_3$ Receptor Antagonists

Developed selective $H_3$ blocker has been investigated by a series of biaryl derivatives. A small library of 49 biphenyl-O-propylamine amides were synthesized as singletons in solution. Synthesized products were purified by using HPLC-MS technique and assays were performing on rat cortex $H_3$ receptors and in a binding experiment, using cloned human $H_3$ [12].

### *Combinatorial Lead Optimization of Dihydrofolate Reductase Inhibitors*

The enzyme like DHFR i.e., dihydrofolate reductase has been proven target for chemotherapy. Recently, work has been done on improving the pharmacokinetic properties of DHFR inhibitors. In solution a library of 1392 compound was synthesized. The compounds were evaluated for inhibition of human DHFR and the bacterial enzymes [12].

### *Synthesis of Peptoids*

Peptoids may be synthesized either by oligomers synthesis 'Full monomer' or 'Sub monomer' [12].

### *"Diversomers": An Approach to Nonpeptide, Non-oligomeric Chemical Diversity*

The formation of benzodiazepine library **(Figure 12)** of forty members was done by treatment of five amino acid resins with each of eight 2-aminobenzophenone imines.

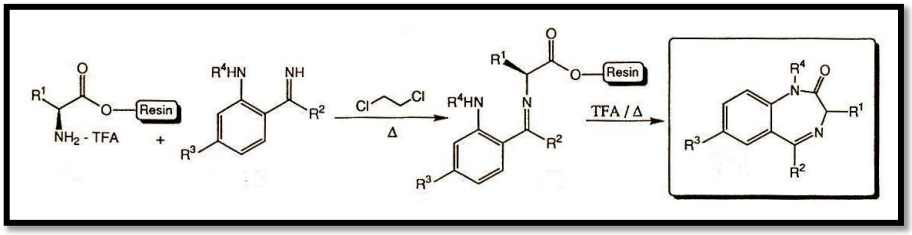


**Figure 12.** Pathways for synthesis of benzodiazepines.

By using same method, small library of hydantoins was formulated **(Figure 13)** by deprotection, each eight amino acid resins treated with each of five isocyanides to give which was then treated with a protic acid and refluxed to remove all protecting group [13].

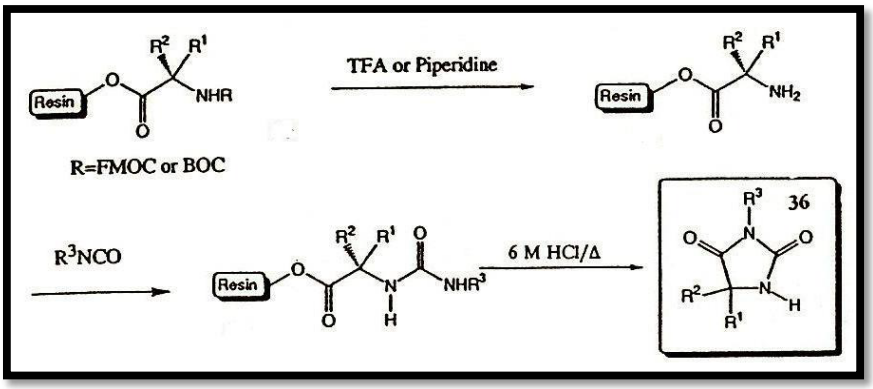


**Figure 13.** General pathways for synthesis of hydantoins.

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p-ISSN:2322-00

***Synthesis of Peptidomimetic Inhibitors for The Hepatitis C Virus $NS_3$ Protease***

This synthesis of peptidomimetic inhibitors for the Hepatitis C virus $NS_3$ protease is explained in **Figure 14** [13].

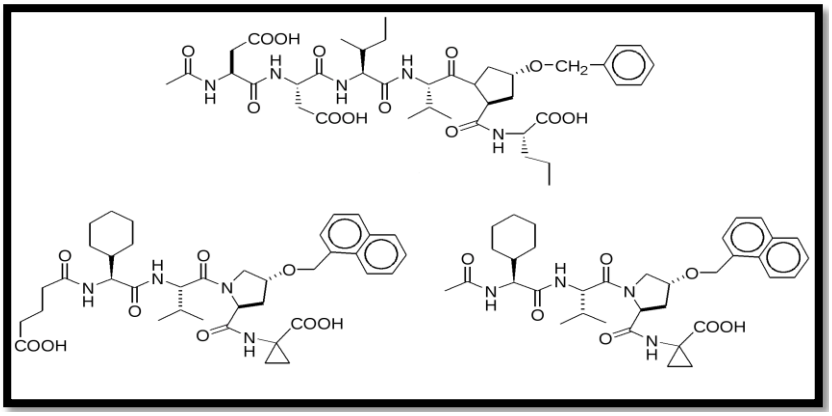

**Figure 14.** Inhibitors for the Hepatitis C virus $NS_3$ protease.

***Synthesis of Piperazinedione Combinatorial Library***

Gordon and Steele have reported the synthesis of a prototype library of 1000 trisubstituted piperazinedione (diketopiperazines, DKPs) by a sequence of three key steps: a novel solid-phase reductive alkylation, acylation by a second amino acids and cyclization to the DKP products [13].

***Combinatorial Lead Optimization of Neuropeptide FF Antagonists***

The tripeptides Pro-Gln-Arg-$NH_2$, derivatized at the secondary amino group of proline residue with (5-dimethylamino)-1-naphthalenesulfonyl (dansyl-PQR-$NH_2$), antagonize the central anti-opioid action of neuropeptide FF in animals after systemic administration **(Figure 15)**. For a combinatorial optimization to improve efficacy, libraries focused on the possible replacement of the glutamine residues and proline of this lead compound were obtained by a solid phase by using methoxybenzyl hydrazine resin and Rink amide, split and- mix method with coded amino acids as building blocks [13].

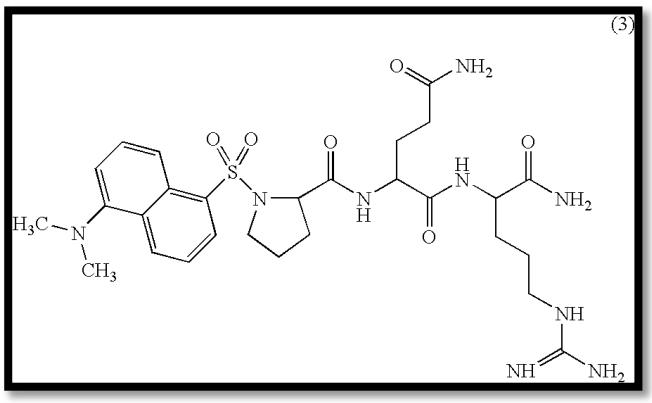

**Figure 15.** Dansyl-Pro-Gln-Arg-NH2.

***Non-peptidyl Library of Sulfonamides***

A new pathway for the synthesis of sulfonamides were showed in **Figure 16** [13].

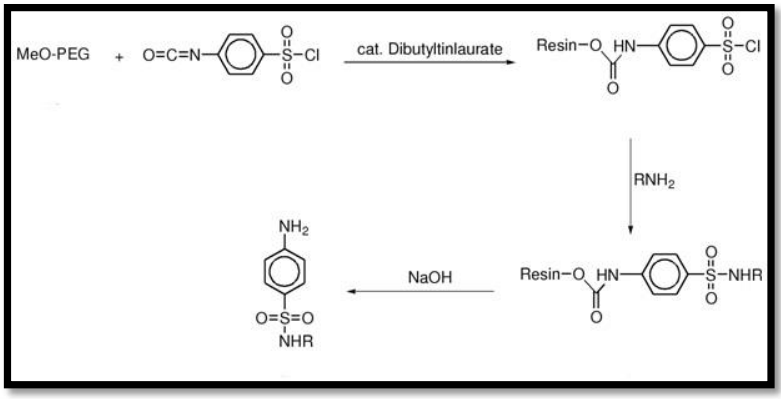

**Figure 16.** Pathway of synthesis of sulfonamides.

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***Generation of Benzodiazepine Library***

The benzodiazepines library was synthesized by different chemical families and on a solid support by the connection of three building blocks. Attachment of carboxyl derivative or 2-aminobenzophenone hydroxy to the support using an acid cleavable linker [(N-hydroxymethyl) phenoxy acetic acid] [12].

***Construction of a "100-Member DHP Library"***

Most successful examples being the calcium channel blocker antihypertensive drugs such as Nimodipine, Nifedipine, Nitrendipine. showed in the **Figure 17** [13].

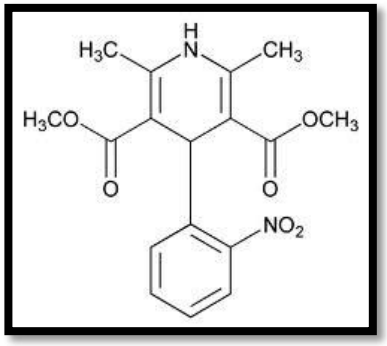


**Figure 17.** Nifedipine.

**Synthesis of Piperazinedione Combinatorial Library**

Gordon and Steele have reported the synthesis of a prototype library of 1000 trisubstituted piperazinedione (diketopiperazines, DKPs) by a sequence of three key steps: a novel solid-phase reductive alkylation, acylation by a second amino acids and cyclization to the DKP products [13].

**Compounds that Activate the Mouse Melanocortin-1-Receptor Identified by Screening a Small Molecule Library Based Upon the β-Turn**

A library of 951 compounds based upon the β-turn motif. The results of the library screening process are consistent with the hypothesis proposing that a β-turn conformation involving the melanocortin "Phe-Arg-Trp" core amino acids provides the key recognition element. This library was synthesized by using amino methylated resin beads coupled with S-acetyl-2-mercapto-2-methyl propionic acid to give compound which was used as a starting material for the preparation of heterocyclic β-turn mimetics [13].

**Synthesis of Peptoids**

Some of the polypeptides of polypeptide libraries were found to be potent inhibitors for enzymes like kinases and proteases useful in treatment of AIDS and cancer, but these peptides have a poor bioavailability and unfavorable pharmacokinetics properties. So, the focus has been shifted on developing synthetic peptide-mimetics like peptoids. Peptoids may be synthesized either by 'full monomer oligomers synthesis' 'Sub monomer oligomers synthesis' [12].

**A Strategy for Preparing Encoded One Bead-One Compound Cyclic Peptide Libraries**

A new technique for making a one bead-one compound cyclic peptide library, in which every bead contains a small proportion of linear peptide that can be readily sequenced by mass spectrometry. The one bead-one compound approach uses routine solid-phase strategies for synthesis combined with a split and mix step between the addition of each amino acid [14].

**Synthesis of A Library Of 2(1h)-Pyridones Via Rhodium-Catalysed Isomunchones**

Library of 2(1h)-Pyridones via Rhodium-Catalysed Isomunchones This approach employs the rhodium-catalysed insertion of a diazo precursor to generate the intermediate isomunchone, which readily undergoes a dipolar cycloaddition with an olefin to generate the fused 2-(1H)-pyridone following decomposition of the intermediate [15].

**An Efficient Method for Making Azido Solid Supports**

An easy and efficient method for the generation of an azido-derivatised resin using imidazole-1-sulphonyl azide. Click chemistry, and in particular the copper-catalyzed azide-alkyne cycloaddition (CuAAC) has become a highly reliable and frequently used synthetic transformation. CuAAC reactions produce 1, 4-disubstituted 1, 2, 3-trizoles [16].

**A New and Efficient Multicomponent Solid-Phase Synthesis Of 2-Acylamino Methylthiazoles Using Rink Amide o Resin**

Thiazoles are assembled in a one-pot MCR of a aldehyde, 3-(*N*, *N*-dimethylamino)-2-isocyanoacrylate, thiocarboxylic acid with a resin-bound primary amine [17].

**High Throughput Screening**

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- High Throughput Screening (HTS) is the process of assaying a large number of potential effectors of biological activity against targets (a biological event). The methods of HTS are applied to the screening of combinatorial chemistry, genomics, protein, and peptide libraries.
- The goal of HTS is to accelerate drug discovery by screening large libraries often composed of hundreds of thousands of compounds (drug candidates) at a rate may exceed 20000 compounds per week.
- This technique will focus on various assay adaptation, robotic equipment, and implementation strategies that allow HTS programme to be successful. Ultra-High Throughput Screening (UHTS) issues (testing of 100000 compounds per day) will also be discussed.
- Reducing the costs, further improving screening throughput and reduced the manipulation steps, also this culminates today in ultra-high-throughput methodologies [18,19].

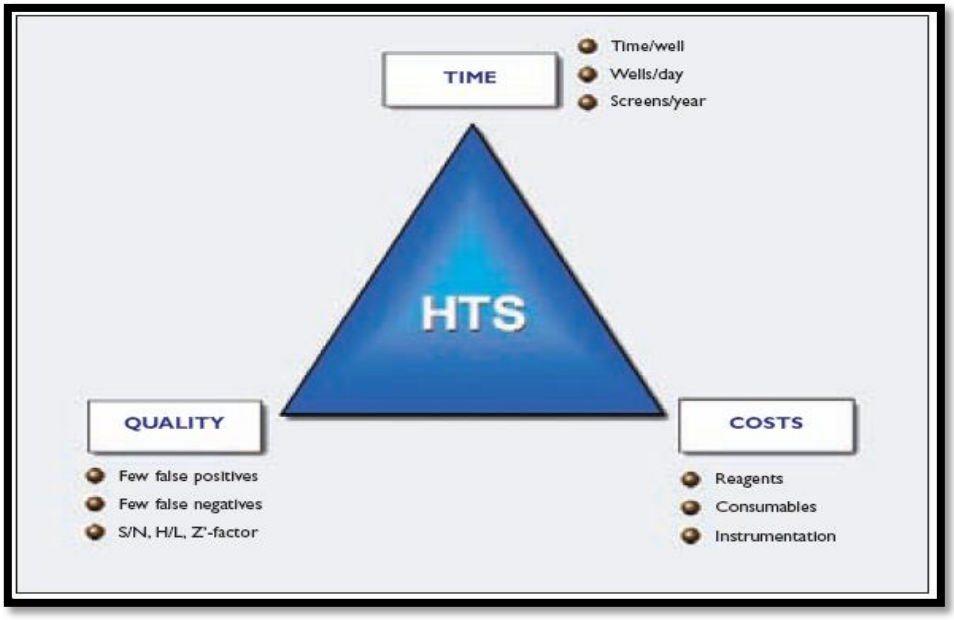


**Figure 18.** High Throughput Screening.

The optimization process for successful high-throughput screening (HTS; "magic triangle of HTS"). The **Figure 18** shows the key success factors for modern lead discovery via HTS—namely, time, costs, and quality. As can be seen in the **Figure 18**, all 3 factors are closely inter-digitated, and every change on either one of these factors influences the setup of all the other factors as well. Optimal lead discovery by HTS finds the right balance between these different elements. S/N, signal/noise; H/L, high/low.

## COMBINATORIAL CHEMISTRY AND Quantitative Structure-Activity Relationships (QSAR)

- Combinatorial chemistry and high-throughput screening this is method which is gain attention from the screening of combinatorial libraries and Virtual filtering.
- QSAR studies can reduce the cost of the drug entity in clinical trials by screening of the combinatorial libraries. Virtual screening can eliminate compounds with predicted harmful, toxic of poor pharmacokinetic properties.
- Techniques include linear methods such as partial least squares. Remain popular method, and classical non-linear methods. However, the need for accurate and rapid, assessment of huge compounds is shifting the attention to novel techniques from machine learning fields and pattern recognition.
- The chemoinformatic techniques serve on QSAR model analysis. This field with established successful history and methodology. From this outlining their usefulness in identifying the general scheme of model and high-throughput screening.
- Chemoinformatic methods under QSAR analysis are in advancement. Well-established techniques, giving successful result [20].

## CONCEPTS OF COMBINATORIAL CHEMISTRY AND COMBINATORIAL TECHNOLOGIES

- Combinatorial Technology and Combinatorial Chemistry is a new field joining computer assisted combinatorial chemistry with synthesis of chemical libraries followed by automated screening.

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- The main purpose is to generate thousands structurally diverse compounds as maximizing their diversity, libraries, which are then considered in an experimental screening and synthesis on the basis of their properties.

- The important issue related to all important steps of concepts or technology in a multidisciplinary and single approach. Pharmaceutical industry did in its entire history than this technology already produced more new compounds in just a few years [21].

## ADVANTAGES AND DIS-ADVANTAGES OF COMBINATORIAL CHEMISTRY

**Advantages**

- Rapid synthesis: Libraries created using combinatorial synthesis require many fewer reaction steps. As a result, the time synthesize a comprehensive library is significantly less using the combinatorial approach.

- Large number: A large diverse chemical library derived from combinatorial synthesis provides a better chance for generating new leads against the numerous diverse targets that are emerging from genomic analysis.

- Richer data from screening: Medicinal chemists are guided through the optimization process by structure activity relationship. A library that contains a great number of active molecules and their analogs provides the chemists with a better roadmap when deciding on next step in optimization; combinatorial libraries typically result in more active hits and thus richer structure activity relationship data to guide optimization.

- Increased likelihood of success: Large libraries increase the chance of new lead discovery. In addition, medicinal chemistry knowledge of desirable drug characteristics is incorporated in the design of both combinatorial libraries and parallel synthesis compounds. Combining size with careful design increases the likelihood that compounds discovered upon initial screening will be potent, selective and bioavailable, thus minimizing the time, efforts and expense of optimization.

- Broader patent protection: Large combinatorial libraries allow researchers to document activity of a large number of compounds. This documentation is useful in seeking broad patent protection which could potentially be useful in preventing or minimizing competitors attempts to develop competitive “me too” drugs.

**Disadvantages**

- In this study, there is difficult to characterize the identification of unexpected or un wonted product combination there is difficult to analyse will cause problems.

- Difficulty of confirming the degree to expected chemistry and substrate molecule is major problem in the combinatorial organic synthesis.

- When you’re doing the solid phase synthesis there is limit to the chemistry. Every reaction steps have to be carefully planned, and after reaction is not available because the chemistry affects the resins [4].

## CURRENT SCENARIO OF COMPANIES USING COMBINATORIAL DRUG DESIGN

- An increasing demand for new drugs, together with ever present economic pressure, has led pharmaceutical companies to invest in combinatorial chemistry to accelerate the drug discovery process.

- However, solution phase synthesis, sometimes in combination with polymer bound reagents or scavenger reagents, offers significant advantages; the range of applicable chemistry is much broader and most problems associated with solid phase synthesis are not encountered.

- For small, focused libraries, automated parallel synthesis in liquid phase is the most cost effective strategy. The building block approach to library synthesis via novel building blocks uses conformational restricted templates, having at least three sites of diversity.

- The most efficient optimization of lead structures is performed by application of intelligent selection and filter function; in addition, affinity estimation, neural networks, genetic algorithms and pattern recognition methods are applied. However, such strategies require the synthesis of “random access” chemical libraries instead of today’s systematic combinatorial libraries.

- Due to the increase in importance of such libraries, automate purification is now an interested process in the production of compound for biological testing. All steps can be automated, from the input of impure compounds in certain format to the output of pure compounds in the same formats. Such libraries also pose a challenge to the analyst to provide meaningful information about them. A High Throughput Organic Chemistry (HTOC) process has been design to transfer crude reaction mixtures to purified compounds of known identity and weight.

## COMBINATORIAL CHEMISTRY: A STRATEGY FOR THE FUTURE

- Combinatorial technologies offer significant advances over traditional scientific research methodologies. In particular, their high-speed approach promises faster results at considerably lower costs than conventional techniques.

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- The globalization of the drug market and the need to swiftly uncover treatments for an ever expanding roster of identifiable diseases are further bolstering demand of combinatorial chemistry. With its ability to offer higher quality leads in the testing phase itself, combinatorial chemistry constitutes a powerful tool for drug discovery and development.
- The seminal human genome project is also expanding the use of combinatorial searches. Computerized scrutiny of a projected 30,000 genes and thousands of proteins is expected to yield information on hitherto unidentified drug targets.
- Combinatorial technologies alone are expected to be able to efficiently process such a mass of information.
- With time and money at a premium, the trend is toward collaborative ventures between drug and biotechnology companies, as the former seek to speedily usher novel and superior drugs into the market. With outsourcing R and D needs and cost sharing being the order of the day, biotech companies are increasingly eager to muscle their way into this lucrative market.
- Now a day's microwave heating is becoming more popular as a means to reduce reaction times and reagent requirements in combinatorial syntheses.
- Combichem techniques are being used as a basic research tools to determine the function of enzymes—a key goal in the field of proteomics and to identify new enzyme inhibitors. And deconvolution methods—technique used to identify active compounds in libraries—continue to refine.
- A new technique-Dynamic Combinatorial Chemistry (DCC) has been introduced. A technique in which a molecular target compounds that can interconvert with each other chemically [22].

## CONCLUSION

- The early years of combinatorial chemistry suffered from an excess of hype, and a major victim was natural-product screening.
- As combinatorial chemistry matures, important and sophisticated design strategies have evolved that are based upon natural products.
- In the coming years, it will be interesting to see if such diversity-oriented syntheses are adopted by big pharma and commercial suppliers of compound libraries, in an effort to enrich currently unfilled chemical space in HTS collections.
- In 1980 and 1990 researcher established combinatorial chemistry it is important discipline has infiltrated and rewrite every sub discipline with modern drug discovery and has impact.
- Application of combinatorial chemistry has chemical lead optimization high throughput screening paradigms, library purification, revolutionized high, post purification sample handling and chemical lead optimization also in vivo and in vitro drug metabolism and P'cokinetic assay.
- Growth of advance combinatorial chemistry is increasing very rapidly over past 10 years. This method has been considered as important advancement in medichem and its utilizes widely in drug discovery.
- Pharmasector must require clever research work to stand in competitive market. And combinatorial chemistry provides higher product within economic cost.
- When optimization of a lead or aim of discovery is broad then combinatorial chemistry is useful for integration of screening and synthesis.
- This technique defiantly useful to finding of new drug molecule with lowest coast associated with research.
- Application of combinatorial chemistry can be applied to various new drug targets. Also within very short time process of drug development is perform by using combinatorial library and in several preclinical studies.
- From above study, we understand that this method is obviously helpful in development of new drug molecule at lower expenses.

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