https://www.wjcmpr.com

WORLD JOURNAL OF CURRENT MEDICAL AND PHARMACEUTICAL RESEARCH

Review Article Open Access

REVIEW ON COMBINATORIAL CHEMISTRY

Akkimi Padma[1*], Basu Venkateswara Reddy[2], S.Meena[3], Sk.Shajaha[4].

Department of pharmaceutical chemistry, Sankarreddy Institute Of Pharmaceutical Sciences, Salakalaveedu(v), Bestawaripeta (m), Prakasm(dist), Pin-523370.

Abstract

Combinatorial chemistry is one of the advanced method of synthesize the large number of molecules in short period of time. Synthesize the million number of same molecules are different molecules at a time. This method was fast and economic, then increase the competition between newer drugs in market. The present review describes that introduction about combinatorial chemistry, combinatorial library, techniques used in combinatorial chemistry and applications. Most commonly used combinatorial techniques are solid phase synthesis (in this technique resin beads, pins and chips are used as solid support, parallel synthesis, mixed combinatorial synthesis and solution phase synthesis. This technique was used in many areas such as pharmaceutical chemistry, biotechnology and agro chemistry. In combinatorial chemistry created large molecules can be detected efficiently.

***Keywords*:** Combinatorial chemistry, combinatorial library, Solid phase synthesis, Solution phase synthesis, Parallel synthesis.

***Corresponding Author:** A. Padma,Assistant professor,Sankar Reddy Institute of Pharmaceutical sciences, Salakalveedu(v), Bestavaripeta(M), Prakasam(Dist),pin code -523370, Andhra Pradesh, India.

Email: akkimipadma@gmail.com

Article History *Received: 021.01.2019, Accepted: 25.01.2019, Published: 28.02.2019.*

Introduction

Combinatorial Chemistry as a valuable tool in drug discovery and material science. It has turned traditional chemistry upside down. It required chemists not to think in terms of synthesizing single, well-characterized compounds but in terms of simultaneously synthesizing large populations of compounds[1]. It also required that those people involved with information management and computational chemistry systems address these same issues as the chemists. It is a valuable tool in drug discovery and material science[1,2].The basic principle of combinatorial chemistry is to prepare a large number of similar compounds at the same time instead of synthesizing compounds in a conventional one at- a-time manner. The characteristic of combinatorial synthesis is that different compounds are generated simultaneously under identical reaction conditions in a systematic manner, so that ideally the products of all possible combinations of a given set of starting materials (termed building blocks) will be obtained at once[3,4]. Combinatorial chemistry is a new method developed by academics and researchers to reduce the time and cost of producing effective, marketable and competitive new drugs. The collection of these finally synthesized compounds is referred to as a combinatorial library[5].

Advantages

- ✓ **Fast:** Combinatorial approach can give rise to millions of compound in same time as it will take to produce one compound by traditional method of synthesis .
- ✓ **Economical**: A negative result of mixture saves the effort of synthesis, purification & identification of each compound
- Easy Isolation purification & identification of active molecule from combinatorial library is relatively easy.
- ✓ **Drug Discovery**: Mixed Combinatorial synthesis produces chemical pool. Probability of finding a molecule in a random screening process is proportional to the number of molecules subjected to the screening process.
- ✓ **Drug Optimization**: Parallel synthesis produces analogues with slight differences which is required for lead optimization

Disadvantages

- ✓ Efficiency is highly affected by compound's size, solubility and function group.
- ✓ Synthesized Compounds present in Achiral of Racemic form.

Fig 1: Steps involved in drug design

Basic concept in Combinatorial Chemistry

It means Preparation of a large number of different compounds at the same time and High throughput-screening provides the most promising substances.

Conventional reaction: A + B ----------> A-B

Combinatorial Chemistry: A (1-n) + B(1-n) ----------> A(1-n) - B(1-n)

Combinatorial libraries

Definition: It means collection of finally synthesized compounds. Compound size depends on the number of building blocks used per reaction and the number of reaction steps, in which a new building block is introduced. In every time 10^2up to 10^5 compounds were synthesized[8].

Fig 2: Combinatorial library

Scaffold- based library: It contain core structure, which all compounds have library is common.

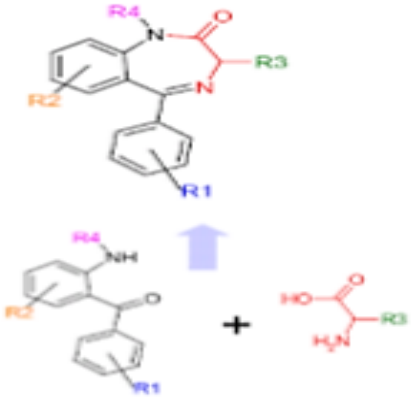

Fig 3: Example of Scaffold-based library

Above Scaffold can consist of several single building blocks (here: Amino acid and Amino benzophenone).

Back –bone based libraries: It means collection of synthesized nucleic acids and carbohydrates.

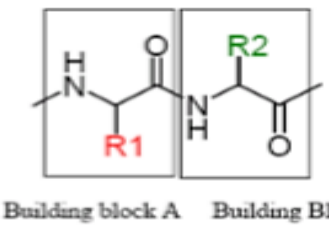

Fig 4: Example of back bone based library

Random libraries	Focused or targeted libraries
Multiple libraries	Template –Scaffold library
Many targets	One target
Highly diverse	High structural similarity
Mixture of compounds	Single compounds
>5000 compounds	<< 5000 compounds
Solid phase synthesis	Synthesis in solution, solid phase
Non purified compounds	Pure compounds
On bead screening, if possible	Screening in solution

Fig 5: Drug discovery strategies in conventional &combinatorial chemistry

Techniques of combinatorial chemistry

- ✓ Solid phase synthesis
- ✓ Parallel synthesis
- ✓ Mixed combinatorial synthesis
- ✓ Solution phase synthesis

Solid phase synthesis

In this technique reactants are bound to a polymeric surface and modified whilst still attached. Final product is released at the end of the synthesis. Various types of linkers and resin beads are act as a solid support. Most commonly used solid supports are partially cross-linked polystyrene beads, Sheppard's polyamide resin, Tentagel resin, Beads, pins and functionalised glass surfaces[9,10].

Advantages

- Beads can be mixed and reacted in the same reaction vessel
- Specific reactants can be bound to specific beads
- Products formed are distinctive for each bead and physically distinct
- Excess reagents can be used to drive reactions to completion
- Excess reagents and by products are easily removed
- Reaction intermediates are attached to bead and do not need to be isolated and purified

- Individual beads can be separated to isolate individual products
- Polymeric support can be regenerated and re-used after cleaving the product
- Automation is possible

Method

Resin beads must be able to swell in the solvent used, and remain stable. The reactions occur in the bead interior.A molecular moiety which is covalently attached to the solid support, and which contains a reactive functional group attachment of the first reactant. The link must be stable to the reaction conditions in the synthesis but easily cleaved to release the final compound. Different types linkers are available depending on the functional group to be attached and the desired functional group on the product. Resins are named to define the linker e.g. Merrifield, Wang, Rink[11].

Merrifield linker: It is suitable for peptide products.

Wang resin: It is suitable for attachment and release of carboxylic acids.

Rink resin: It is suitable for the attachment and release of carboxamidde.

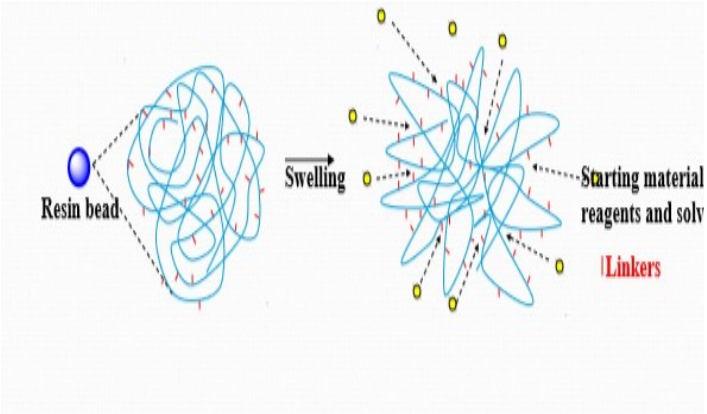

Fig 6: Mechanism of solid phase synthesis

Fig 7: Equipment used for Solid phase synthesis

Parallel synthesis

Parallel synthesis used to a standard synthetic route to produce a range of analogues, with a different analogue in each reaction vessel, tube or well and easily identify the known structure. This method was producing a large number of analogues in drug optimization. Parallel synthesis was done for the two methods. They are Houghton's Tea Bag Procedure and automated parallel synthesis[12].

Houghton's Tea Bag Procedure

In this method each tea bag contains resin beads and is labeled. Separate reactions are carried out on each tea bag and combine tea bags for common reactions. A single product is synthesized within each teabag, different products are formed in different teabags. This method was cheap and possible for any lab and manual procedure. It is not suitable for the producing large quantities of different products[12,13]

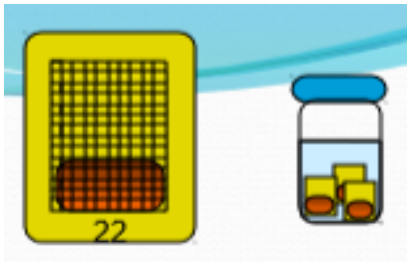

Fig 8: Houghton's Tea Bag

Automated parallel synthesis

Automated synthesizers are available with 42, 96 or 144 reaction vessels or wells. Resin beads or pins are producing solid phase support to the drug synthesis. Chemical reactions and work ups are carried out automatically in reaction vessels. Same synthetic route used for each vessel, but different reagents are used then produce the different products per each vessel.

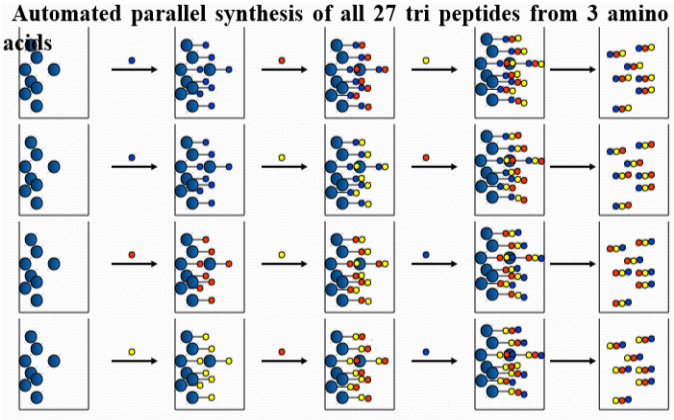

Fig 9: Automated parallel synthesis

Mixed combinatorial synthesis

In this method use of standard synthetic route to produce a large variety of different analogues 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 finding a lead compound. It is capable of synthesizing large

numbers of compounds quickly. Inactive mixtures are stored in combinatorial libraries and active mixtures are studied further to identify active component[14]. Example: Combinatorial procedure involves five separate syntheses using a mix and split strategy.Synthesis of all possible dipeptides using 5 amino acids then produce 25 separate analogues.

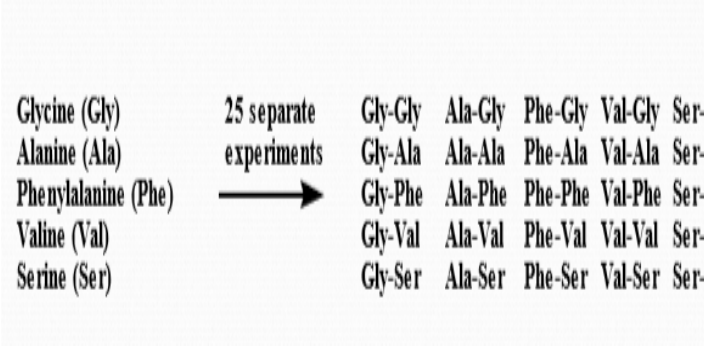

Fig 10: Mixed combinatorial synthesis

Other methods

Multi pin synthesis: The reaction vessel consist of brush like array of pins, at the end of it consist of bead with suitable linker, here the synthesis take place. It is inserted into the plates where the reagents and solvents kept in reaction vessel. Reagents and solvents are continuously changed in the time of reaction[15].

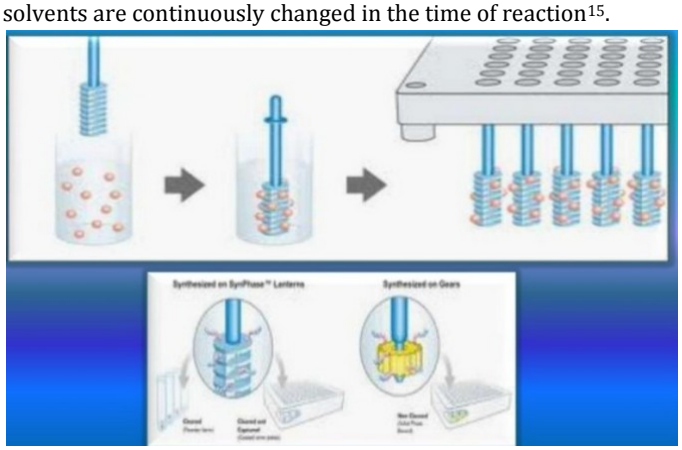

Fig 11: Multi pin synthesis

Solution phase synthesis

Solution phase synthesis is most commonly used synthesis for the production of new molecules. Isolation of the product is the biggest challenge in this synthesis. Most of the organic reactions occurred in solution. For these reason there has been much interest in the solution phase synthesis. The main advantage of this method difficulty to remove unwanted impurities in each step of synthesis[16].

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 Nano moles).
- ✓ 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.

Example

R-CO-Cl + R^I-NH2----------> R-CO-NH-R^I +HCl

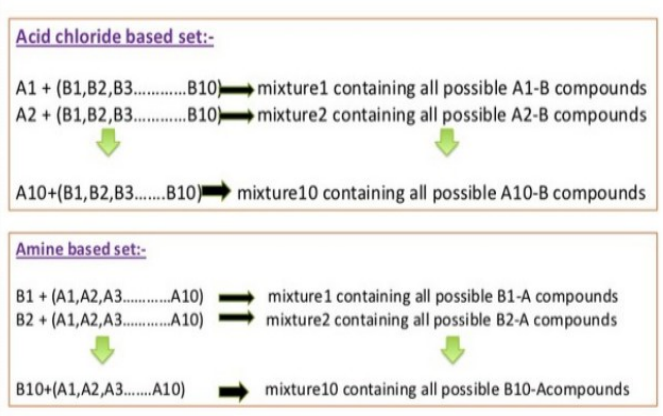

Fig 12: Example of solution phase synthesis

Applications of Combinatorial chemistry

- ➢ Applications of combinatorial chemistry are very wide Scientists use combinatorial chemistry to create large populations of molecules that can be screened efficiently.
- ➢ By producing larger, more diverse compound libraries, companies increase the probability that they will find novel compounds of significant therapeutic and commercial value.
- ➢ Provides a stimulus for robot-controlled and immobilization strategies that allow high-thrughputand multiple parallel approaches to drug discovery[18,19].
- ➢ **High Throughput Screening (HTS)**: It 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 programe to be successful. It reducing the costs, further improving screening throughput and reduced the manipulation steps, also this culminates today in ultra-high-throughput methodologies[20,21].

Conclusion

The present review concluded that importance of combinatorial chemistry in production of large number of molecules. This technique was commonly used in pharmaceutical industry for identification and structural characterization of new compounds in short period of time. By optingthe combinatorial chemistry to create the thousands of molecules per week. Solid and solution phase synthesis methods are most useful for the production of combinatorial libraries because all the synthetic transformations successfully applied to solid phase and with the development of high-throughput screening, libraries are widespread in pharmaceutical and agricultural chemistry.

References

1. S. Borman. Combinatorial Chemistry. 2002; 80(45):43-57.
2. J. H. Block, J. M. Beale, Ed. 11th, Lippincott Williams and Wilkins, pp. 43-49 (A wolters kluwer company: Philadelphia).
3. A. Burger's. a wiley-interscience publication. (Ed. Abraham DJ). vol. 2, Ed. 6th, 1-36 (Virginia: Midlothianpp).
4. Z. Yu, M. Bradley. Current Opinion in Chemical Biology. 2002: 6: 347–352.
5. V. M. Mirsky, V. Kulikov, Q. Hao, O. S. Wolfbeis. Multiparameter High Throughput Characterization of Combinatorial Chemical Microarrays of Chemosensitive Polymers. Macromolec. Rap. Comm. 2004; 25: 253-258.
6. H. Koinuma et al. Combinatorial solid state materials science and technology. Sci. Technol. Adv. Mater. 2000;1.
7. Andrei Ionut Mardare et al. Combinatorial solid state materials science and technology. Sci. Technol. Adv. Mater.2008; 9.
8. J. N. Cawse et al. Progress in Organic Coatings. 2003;47(2):128-135.
9. Shaikh SM, Nalawade, Shete AS and Doijad RC.A Review on Combinatorial Chemistry. RRJCHEM. 2017; 6(2): 14-26
10. Anas Rasheed and Rumana Farhat. Combinatorial Chemistry: A Review. IJPSR.2013; 4(7):2502-16.
11. AK Mishra, A Gupta, AK Singh, P Bansal. Combinatorial chemistry and its application - a review. Int J of Chem and Anal Sci. 2010;1(5):100-105.
12. Terrett NK. A Strategy for Preparing Encoded One Bead-One Compound Cyclic Peptide Libraries. Curr Lite Highlights Combinat Chem. 2013;15:45-47.
13. Combinatorial Methods for High-Throughput Materials Science, MRS Proceedings Volume 1024E, Fall 2007.
14. Combinatorial and Articial Intelligence Methods in Materials Science II, MRS Proceedings Volume 804, Fall 2004.
15. QSAR and Combinatorial Science, 24, Number 1 (February 2005).
16. Pandeya SN and Thakkar D. Advances in Contemporary Research, Combinatorial Chemistry: A Novel Method In Drug Discovery And Its Application. Ind J Chem. 2005;44:342-348.
17. Abdel-Hamide SG. Heterogenous Phase as A Mean in Combinatorial Chemistry. Chem. Info. 2007;38:8-24.
18. Englebienne P. High Throughput Screening: Will the Past Meet The Future? Front. In Drug Des Discov. 2005;1:69.
19. Mayr LM and Fuerst P. The Future of High-Throughput Screening. J Biomol Screen. 2008;445.
20. Dudek AZ, et al. Computational Methods In Developing Quantitative Structure-Activity Relationships (Qsar): A Review. Combinat Chem High Through Screen. 2006;9:213-226.
21. Miertus S, et al. Concept of Combinatorial Chemistry and Combinatorial Technologies. Chemistry Listy. 2004;94:1104.
22. Brown D. Future Pathways for Combinatorial Chemistry. J Mol Diver. 1997;2:217.