THE SIGNIFICANCE OF COMBINATORIAL CHEMISTRY IN THE DRUG DISCOVERY

Abstract

The 'Combinatorial chemistry' means the systemic & repetitive co-valent connection for benefit of various building blocks of different array of divergent molecular structures. It is reconsidered, the way by which pharmaceuticals, other chemicals and materials are discovered and developed by this novel technique. It is useful for 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 extensive utilization of novel drug targets. Nowadays, these technologies are commonly implemented in combination with other for discovery projects.

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I. INTRODUCTION

Combinatorial chemistry is systematic and recurring covalent bonding of various chemical entities. The lead finding and development 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 in combinatorial chemistry. In a 'combinatorial preparations', the various number of compounds formed increases 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 use like Particle. In 1927 the basic 'combinatorial chemistry' prototype was first investigated by Eddington. 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. It gives Libraries which consists information of million numbers of molecules within short period of time, for which scientists requires many years to investigate. Preparations of molecules by this way can rapidly lead to enormous particles. Researchers frequently develop a "virtual library," a computer tool, to pick-up the enormous number of structural options. Listing all potential structures with all available data reactants. These "virtual" compounds can number in the thousands to millions in 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 research to fasten the process. The expenses related to creating innovative drugs that are both effective and affordable. By quickening chemical preparations, this approach is having a significant impact on the discovery of new drugs. This powerful technology has started to help pharmaceutical companies to search new drug candidates quickly, save more money in preclinical development and finally change their fundamental approach to 'drug discovery'.

1. History

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 et.al.	Positional scanning
	SM	Ellman	synthesis of Benzodiazepines (Solid-phase)
1993	SM	De Witt	Diversomers (parallel solid-phase synthesis on resin)
1994	SM	Smith	'Indexed library'
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)

II. PRINCIPLE OF 'COMBINATORIAL CHEMISTRY'

Fundamental concept for the investigations is the ability to produce enormous 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 implement the idea of this technique is very important. Basic concept of this research consists of

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

III. COMBINATORIAL CHEMISTRY APPROACH

Combinatorial chemistry covers many ideas for the quick preparations of large, systemic collections of molecules called library. After collection it is screened for the biological activity. At last, most potent compound is point out and mass-produced as a single compound. So it has two stages:

1. Making a 'combinatorial library'
2. Searching the 'potent 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 crystallization, distillation or chromatography. Besides to conventional point of view, It gives the potential to make every combination of compound A_1 to A_n and with compound B_1 to B_n

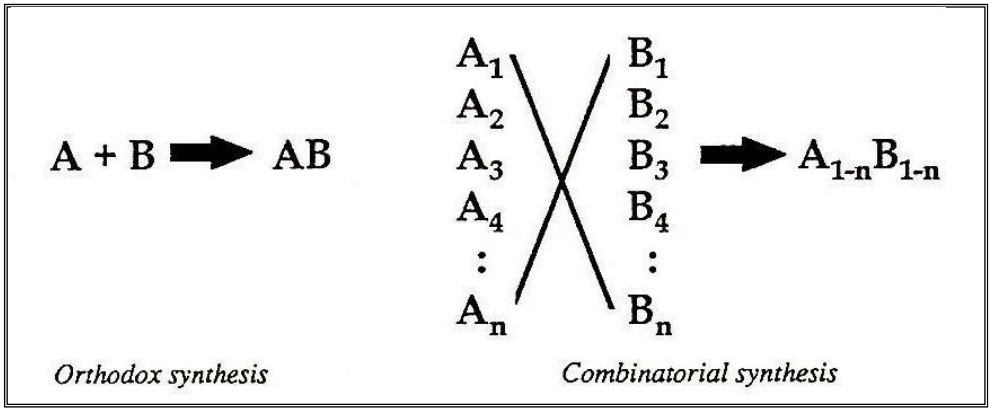

Figure 1: Orthodox Synthesis Vs Combinatorial Synthesis.

Various methods can be used for the manufacture of compounds; they can be prepared by individually in parallel or by many mixtures using solid phase technology or by utilizing solutions. It was found that productivity levels have been greatly increased beyond what has been typical in the last century. It 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 has concluded that this

technique is good technology to investigate new molecules, catalysts and substances than using one drug at one time discovery process.

IV. TYPES OF COMBINATORIAL LIBRARIES

1. The 'Scaffold-based' Libraries: collection is based on original molecular Scaffold Ex: Residue is composed of three Amino acids & Amino Benzophenone.
2. The 'Backbone-based' Library Ex: Nucleic acid
3. 02 techniques for generation of libraries are focused libraries & random libraries.

V. COMBINATORIAL CHEMISTRY-METHODS

1. **Solid phase technique:** The reactants is attached to a polymeric surface and developed at the same time attached. Finally the product is moved to the end of the preparation.
   - **Requirements**
     - For solid support resin beads are used.
     - The 'anchor or linker.'
     - 'Bond linking' the substrate to the 'linker.'
     - Able to remain stable at the reaction conditions used in the preparation.
     - Indicate splitting the product from, the linker at the end.
     - Protecting groups used for 'functional groups' which are not taking part in the preparation.
   - **Solid phase tool**
     - Beads must remain stable & it should swell in the solvent.
     - In the interior of the bead maximum reactions takes place.
   - **Anchor or linker**
     - The bond which links a molecule to a solid support
     - Enables linking of reactant
     - Link should easily cleaved & release final compound, remain stable to the reaction conditions in preparation
       E.g. Merifield resin, Tritylchloride resin, Wang resin, Hydroxymethyl resin.
       Amines
       E.g. Boc group using t-butoxy carbonyl group
       Fmoc group using g-fluorenyl methoxy carbonyl group. Carboxylic acids
       E.g. Tertiary butyl ester group Fmster group Tmester group
   - **Advantages**
     - Minimum requirements of reaction vessels.
     - Generation of large quantities of libraries within few minutes.
   - **Disadvantages**
     - Complex mixtures are formed.
     - Deconvolution is required
     - Large quantity of resin beads is required
     - Synergistic effects may be observed during screening, leading to false positives.

2. **Parallel synthesis**
   - **Parallel synthetic method**
     - In this method, in separate vessel, each starting material is required with each building block separately.

- At end of reaction, product is split into 'n' portions before it is reacted with 'n' new building blocks.
- Useful for creating a variety of referents for drug optimization and Structure Activity Relationship

- **Tea bag (houghton's) method**
  - Every tea bag contain bead.
  - Separate reaction is performed in each tea bag
  - Combination of tea bags aimed at exertion up procedure and for common reaction.
  - Within each teabag a single product is prepared.
  - In different teabags various products are formed
  - For many labs it is cheap and accessible.
- 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 responses and effort are carried out
  - Different reagents are used for same synthetic route.
  - In each vessel diverse products formed.

3. Mixed combinatorial preparations

- By means of a standard synthetic route, to yield an enormous variability of different counterpart where every reaction vessel or tube contains a mixture of products.
- The characteristics of the structures, in each vessel are not known by conviction.
- Valuable for searching novel lead compound.

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

4. Solution phase synthesis: This assess usually in the 96-well plate design, it is used in mass transmission for maximum drug innovation programs. There are various solution stage tests are obtainable.

- **Combination of on bead and solution phase screening assay:** It might be beneficial to combine solution part assays with on bead assays to monitor a exact object. Positive beads isolated by this method are more expected to be true positives Eg. The compound beads are split in to 1000 beads per well and a portion of the compound on each bead is free into the solution for biological testing.
- **The multipin method:** In parallel procedures an collection of diverse substances are concurrently prepared. Geysen et al and his associates circulated the first case of parallel synthesis. They have a chain of peptides epitopes in an apparatus prepared for this drive. The multipin apparatus had a chunk of wells aiding as reaction vessels and cover plate with mounted polyethylene rods fitting into well.

- **One bead one compound technique:** In this method for each possible structure a precise amount of beads is allotted in the library; those beads contain only molecules of the certain library member.
- **Iterative deconvolution:** It is used when combinatorial chemistry was ongoing. Each

group has beads bearing a diversity of compounds, but a given structure only looks in one of the groups.

- **Subtractive deconvolution:** This is mainly valuable for 'QSAR-type studies' in which, a cl group is situated at numerous positions on a phenyl ring.
- **Detection by bogus-coin:** This begins with producing & screening the whole library as a single mixture.
- **Orthogonal pooling:** It specifies vertical/uncorrelated. In this type of assembling, we allot the functional groups to be measured into sets of libraries like A, B, C etc., which can contain mixtures of the similar compounds.

VI. IMPORTANCE OF COMBINATORIAL CHEMISTRY IN DRUG DISCOVERY

1. This technique is used for formation of large number of biologically potent design and their mixtures, also quickly transmit them for desirable properties.
2. It reduces time and it is cheaper method.
3. Drug can easily present in very less time for clinical trials due to this methodology
4. Development of newer molecule is very crucial and difficult job in pharmaceuticals.
5. In medical field there always need newer chemical entities with divergent pharmacophoric stuff
6. New drugs should cure diseases and should be non-toxic in nature
7. Newer compound should not become ineffective to resistant strains of microorganisms.
8. Combinatorial chemistry have bestow to life processes and attempt to increase the quality of life and also development of society.

VII. CHALLENGES IN COMBINATORIAL CHEMISTRY

1. To design and toning a target with the diversity-producing chemical, scheme-including the choice to produce independently or as a combination.
2. To Comfort that the preferred choice of molecule is manufactured.
3. To Judge which compound is active within combinations that test "active"-deconvolution of the mixture.
4. Manufacturing strong outline for fastening the produced molecule in the incident of solid-phase preparation.
5. To manage the data concerning to the production and analyses.

VIII. FUTURE SCOPE OF 'COMBINATORIAL CHEMISTRY'

1. In the last two decades it has observed an blast in the investigation and acquisition of Combinatorial techniques
2. Pharmaceutical chemist's belief that this methodology will allow the productive and cost-efficient origination of compounds as well as drug molecules.
3. It is becoming an ideal part of medicinal chemists instrument
4. It will make major effect on the path drug molecules discovery.

IX. CONCLUSION

1. Many Pharmaceutical/Biotechnology companies have the target to design and form highly varied molecular libraries to be screened on selected targets.

2. This technique has major impact on identification of new ideas
3. Many compounds have progressed into clinical trials
4. These techniques are used in diagnostics, catalysis, down-stream processing etc.

REFERENCES

[1] Fodor SP, Read JL, Pirrung MC, Stryer L, Lu AT, Solas D, Light-directed, spatially addressable parallel chemical synthesis. Science, 1991; 251: 767-73. PMID 1990438.
[2] E.V.Gordeeva et al. "COMPASS program - an original semi-empirical approach to computer-assisted synthesis" Tetrahedron, 1992; 48: 3789.
[3] X. -D. Xiang et al. "A Combinatorial Approach to Materials Discovery" Science, 1995; 268: 1738.
[4] J.J. Hanak, J. Mater. Sci, Combinatorial Characterization, 1970; 5: 964-971.
[5] Combinatorial methods for development of sensing materials, Springer, 2009. ISBN 978-0-387-73712-6.
[6] 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.
[7] Andrei IonutMardare et al. "Combinatorial solid state materials science and technology" Sci. Technol. Adv. Mater., 2008; 9: 035009.
[8] Applied Catalysis A, 10 November, 2003; 254(1): 1-170.
[9] J. N. Cawse *et al*, Progress in Organic Coatings, August, 2003; 47(2): 128-135.
[10] Combinatorial Methods for High-Throughput Materials Science, MRS Proceedings Volume 1024E, Fall, 2007.
[11] Combinatorial and Artificial Intelligence Methods in Materials Science II, MRS Proceedings, 2004; 804,
[12] Merrifi eld, R. B. Solid phase peptide synthesis. 1. The synthesis of a tetrapeptide. *J. Am. Chem.Soc.* 1963, *85*, 2149–2154.
[13] Leznoff, C. C. The use of insoluble polymer supports in general organic synthesis. *Acc. Chem.Res.* 1978, *11*, 327–333.
[14] Geysen, H. M.; Meleon, R. H.; Barteling, S. J. Use of peptide synthesis to probe viral antigens for epitopes to a resolution of a single amino acid. *Proc. Natl. Acad. Sci. U.S.A.* 1984, *81*,3998–4002.
[15] Houghten, R. A. General method for the rapid solid-phase synthesis of large numbers of peptides: specificity of antigen–antibody interaction at the level of individual amino acids. *Proc.Natl. Acad. Sci. U.S.A.* 1985, *82*, 5131–5135.
[16] Furka, A.; Sebestyen, F.; Asgedom, M.; Dibo, G. Cornucopia of peptides by synthesis. *Abstr.14th Int. Congr. Biochem. Prague, Czechoslovakia* 1988, 47.
[17] Furka, A.; Sebestyen, F.; Asgedom, M.; Dibo, G. General method for rapid synthesis of multicomponent peptide mixtures. *Int. J. Peptide Protein Res.* 1991, *37*, 487–493.
[18] Fodor, S. P. A.; Read, J. L.; Pirrung, M. C.; Stryer, L.; Lu, A. T.; Solas, D. Light-directed, spatially addressable parallel chemical synthesis. *Science* 1991, *251*, 767–773.
[19] Houghten, R. A.; Pinilla, C.; Blondelle, S. E.; Appel, J. R.; Dooley, C. T.; Cuervo, J. H. Generation and use of synthetic peptide combinatorial libraries for basic research and drug discovery.*Nature* 1991, *354*, 84–86.
[20] Pinilla, C.; Appel, J. R.; Blanc, P.; Houghten, R. A. Rapid identifi cation of high affi nity peptide ligands using positional scanning synthetic peptide combinatorial libraries. *BioTechniques* 1992, *13*, 901–905.
[21] Dooley, C. T.; Houghten, R. A. The use of positional scanning synthetic peptide combinatorial libraries for the rapid determination of opioid receptor ligands. *Life Sci.* 1993, *52*, 1509–1517.
[22] Smith, P. W.; Lai, J. Y. Q.; Whittington, A. R.; Cox, B.; Houston, J. G.; Stylli, C. H.; Banks,M. N.; Tiller, P. R. Synthesis and biological evaluation of a library containing potentially 1600

amides/esters: a strategy for rapid compound generation and screening. *Bioorg. Med. Chem. Lett.* 1994, *4*, 2821–2824.

[23] Deprez, B.; Williard, X.; Bourel, L.; Coste, H.; Hyafi l, F.; Tartar, A. Orthogonal combinatorial chemical libraries. *J. Am. Chem. Soc.*1995, *117*, 5405–5406.

[24] Lam, K. S.; Salmon, S. E.; Hersh, E. M.; Hruby, V. J.; Kazmierski, W. M.; Knapp, R. J. A new type of synthetic peptide library for identifying ligand-binding activity. *Nature* 1991, *354*,82–84.

[25] Bunin, B. A.; Ellman, J. A. A general and expedient method for the solid-phase synthesis of 1,4-benzodiazepine derivatives. *J. Am. Chem. Soc.* 1992, *114*, 10997–10998.

[26] Bunin, B. A.; Plunkett, M. J.; Ellman, J. A. The combinatorial synthesis and chemical and biological evaluation of a 1,4- benzodiazepine library. *Proc. Natl. Acad. Sci. U.S.A.* 1994, *91*,4708–4712.

[27] DeWitt, S. H.; Kiely, J. S.; Stankovic, C. J.; Schroeder, M. C.; Reynolds Cody, D. M.; Pavia,M. R. "Diversomers": an approach to nonpeptide, nonoligomeric chemical diversity. *Proc.Natl. Acad. Sci. U.S.A.* 1993, *90*, 6909–6913.

[28] Ohlmeyer, M. H. J.; Swanson, R. N.; Dillard, L. W.; Reader, J. C.; Asouline, G.; Kobayashi, R.; Wigler, M.; Still, W. C. Complex synthetic chemical libraries indexed with molecular tags.*Proc. Natl. Acad. Sci. U.S.A.* 1993, *90*, 10922–10926.

[29] Ni, Z.-J.; Maclean, D.; Holmes, C. P.; Murphy, M. M.; Ruhland, B.; Jacobs, J. W.; Gordon, E. M.; Gallop, M. A. Versatile approach to encoding combinatorial organic syntheses using chemically robust secondary amine tags. *J. Med. Chem.* 1996, *39*, 1601–1608.

[30] QSAR and Combinatorial Science, February, 2005; 24: 1.

[31] J. N. Cawse, Ed., Experimental Design for Combinatorial and High Throughput Materials Development, John Wiley and Sons, 2002.

[32] D. Newman and G. Cragg "Natural Products as Sources of New Drugs over the Last 25 Years" J Nat Prod, 2007; 70: 461.

[33] M. Feher and J. M. Schmidt "Property Distributions: Differences between Drugs, Natural Products, and Molecules from Combinatorial Chemistry" J. Chem. Inf. Comput. Sci., 2003; 43: 218.

[34] E. Campian, J. Chou, M. L. Peterson, H. H. Saneii, A. Furka, R. Ramage, R. Epton (Eds) In Peptides, 1998, Mayflower Scientific Ltd. England, 1996; 131.

[35] V. Nikolaiev, A. Stierandova, V. Krchnak, B. Seligman, K. S. Lam, S. E. Salmon, M. LeblPept. Res., 1993; 6: 161.

[36] Stierandova, V. Krchnak, B. Seligman, K. S. Lam, S. E. Salmon, M. LeblPept. Res., 1996; 7: 191.

[37] D. Newman and G. Cragg "Natural Products as Sources of New Drugs over the Last 25 Years" J Nat Prod, 2007; 70: 461.

[38] Leeson, P. D. et al. "The influence of drug-like concepts on decision-making in medicinal chemistry". Nat. Rev. Drug Disc., 2007; 6(11): 881–890.

[39] John Faulkner D, Newman DJ, Cragg GM. "Investigations of the marine flora and fauna of the Islands of Palau". Nat Prod Rep., February, 2004; 21(1): 50–76.

[40] Hopkins, A. L., Groom, C. R. and Alexander, A. "Ligand efficiency: a useful metric for lead selection". Drug Discovery Today, 2004; 9(10): 430–431.

[41] Ohlstein, E. H.; Ruffolo, R. R.; Elliott, J. D. Drug discovery in the next millennium. *Annu. Rev.Pharmacol. Toxicol.* 2000, *40*, 177– 191.

[42] Drews, J. Drug discovery: a historical perspective. *Science* 2000, *287*, 1960–1969.

[43] Venton, D. L.; Woodbury, C. P. Screening combinatorial libraries. *Chemom. Intell. Lab. Syst.*1999, *48*, 131–150.

[44] Lam, K. S.; Lebl, M.; Krchnak, V. The "one-bead–one-compound" combinatorial library method. *Chem. Rev.* 1997, *97*, 411–448.

[45] Eddershaw, P. J.; Beresford, A. P.; Bayliss, M. K. ADME/PK as part of a rational approach to drug discovery. *Drug Discov. Today*2000, *5*, 409–414.

[46] Brennan, M. B. Drug discovery. Filtering out failured early in the game. *Chem. Eng. News* 2000, *78*, 63–73.

