LIQUID PHASE OF COMBINATORIAL CHEMISTRY-A REVIEW

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Article History: Received:12/07/2020 Revised: 15/08/2020 Accepted: 20/10/2020

Abstract

Combinatorial chemistry is a new methodology by which we can simultaneously synthesize a number of possible compounds that could produce simultaneously a very large number of compounds, called libraries. Combinatorial chemistry involves the rapid synthesis or the computer simulation of a large number of different but often structurally related molecules or materials. Combinatorial chemistry is especially common in CADD (Computer aided drug design) and can be done online with web based software, such as Molinspiration.In the past, chemists have traditionally made one compound at a time.

Key Words: Combinatorial Chemistry, CADD, Nuclear receptors, Synthesizer technology, Parallel synthesis

DOI: 10.48047/ecb/2020.09.10.04

INTRODUCTION

Combinatorial Chemistry is a technology for synthesizing and characterizing collection of compounds and screening them for useful properties was convinced about 20 years ago [1]. Initially, the field focused primarily on the synthesis of peptide and oligonucleotide libraries. In 1990s, the focus of the field changed predominantly to the synthesis of small, drug like organic compounds [2].Many pharmaceutical companies and biotechnology called firms now use it in their drug discovery efforts. Discovery process became a highly parallel one, in which hundreds or even thousands of structures could be synthesized at one time [3]. High throughput screening (HTS) have been performed for their in vitro assays, running assays in 96 well micro tier plates and by using laboratory robotics for pipetting and analysis [4]. Researchers continue to find the ways to further enhance the capabilities of combinatorial chemistry including these developments.

A growing trend towards the synthesis of complex natural-product-like libraries, including the carbohydrate-based libraries, an increased focus on –phase trafficking techniques are used for integrating synthesis with purification, novel strategies for purification and analysis, such as combinatorial use of supercritical fluid chromatography and the application of

combinatorial chemistry to new targets such as nuclear receptors [5]. The goal of combinatorial chemistry able to synthesize purity, chemically analyze andbiologically test all the structures in the library, using few synthetic experiments as possible. Chemistry was first applied to the synthesis of peptides. In 1963 Merrifield introduced the efficient synthesis of peptides on a solid support and resin. Combinatorial chemistry is of two types first a solid phase combinatorial chemistry and second is solution phase combinatorial Chemistry.

HISTORICAL DEVELOPMENT

Combinatorial Chemistry has been invented by Furka (Eotvos Lorand University Budapest Hungary) who described the principle of it, the combinatorial synthesis and a deconvolution procedure in a document that was notarized in 1982 [6]. Combinatorial chemistry is a young science, having only been around approximate 40years. It has been applied to drug design for an even shorter period of time [7]. The origins of combinatorial chemistry can be traced back at least as far as 1963, when biochemistry professor R. Bruce Merrifield of Rockefeller University, New York City developed a way to make peptides by solid-phase synthesis [8]. For his work on solid phase, Bruce Merrifield owned a Nobel Prize in chemistry in 1984. During this time, automated peptide synthesizer technology was in its infancy, and the preparation of individual peptides was a challenge [9]. The field in its modern dimensions only began to take shape in 1980s, when in 1984 research scientist H Mario Geyser, now at Glaxo welcome, Research Triangle Park, N.C., developed a technique to synthesize arrays of peptides on pin-shaped solid supports and in 1985 Richard Horton developed a technique for creating libraries in tiny mesh ―tea bags‖ by solid-phase parallel synthesis [10]. Another early pioneer was Dr. Arpad Furka who introduced the commonly used split- and-pool method in 1988, which is used to prepare millions of new peptides in only a couple of days and also for synthesizing organic libraries [11]. Through the 80s and into the early 1990s, combinatorial chemistry was focused on peptide synthesis and later oligonucleotides synthesis. In the 1990s, the focus of the field changed predominantly to the synthesis of small drug like organic compounds and many pharmaceutical companies use thistechnology for their work.

DIFFERENCE BETWEEN TRADITIONAL AND COMBINATORIAL SYNTHESIS

Parameters	Traditional method	Combinatorial method
1. Reaction	Not so simple	Many a times simpler
2. Extreme conditions at High temperature orpressure	Possible to use	Avoided
3. Use of highly causticreagent	Possible to use	Avoided
4. Use of in ert atmosphere	Possible to use	Avoided
5. Multistep reaction	Possible to use	Avoided
6. Yield of compound	Gives single compound	Gives chemical libraries

PRINCIPLE OF COMBINATORIAL APPROACH:

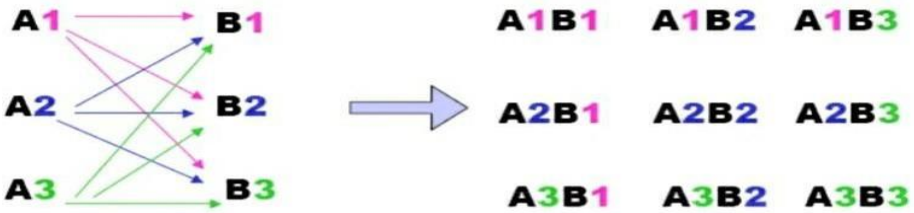
Principle of combinatorial chemistry is of synthesizing large number of different components

at the same time instead of synthesizing compounds in a conventional one at a time manner and then to identify the most promising compounds for further development.

Orthodox synthesis

A + B ⟶ AB

Combinatorial synthesis



Combinatorial approach has two phases

- Creating chemical libraries
- Identification of active ingredients

Creating chemical libraries

Compound 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 physical chemical characteristics, purity, quantity of the compound [12].

Identification of active ingredient

Major challenge in developing library of compounds in screening the library for the activity of chemical species responsible. The goal of producing molecule are 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

COMBINATORIAL LIBRARIES:

Combinatorial libraries are special multicomponent mixtures of small-molecule chemical compounds that are synthesized in a single step wise process [13]. They differ from the collection of individual components as well as from series of compounds prepared by parallel synthesis. It is an important feature that the mixture ensures the very high efficiency of the process [14]. Both reactants can be mixtures and in this case the procedure would be more

efficient. For practical reasons however, it is advisable to use the split-mix method in which one of the two mixtures is replaced by single building blocks (BBs). The mixtures are also important that there are no combinatorial libraries without using the mixture in the synthesis and if a mixture is used in a process inevitably combinatorial library forms. The split-mix synthesis is usually realized using solid support but it is possible to apply it in solution. Since the structure the components are unknown deconvolution methods need to be used for screening [15].One of the most important features of combinatorial libraries is that whole mixture can be screened in a single process. This makes these raspberries are useful in pharmaceutical research. Partial libraries or full combinatorial libraries can also be synthesized. Some of them can be used in deconvolution.

Types of combinatorial libraries:

1. Scaffold-based libraries
2. Backbone-based libraries

Scaffold based libraries:

Core structure, which all compounds of the library have in common. They consist of several single building blocks.

Example: Amino acid, Amino Benzophenone.

Backbone based libraries:

Example: Nucleic acid and carbohydrate.

Functions of Combinatorial libraries:

- Optimization
- Identification

ADVANTAGES OF COMBINATORIAL CHEMISTRY:

- Fast: Combinatorial approach can give rise to millions of components same time as it will take place to produce one component by traditional method of synthesis.
- Economical: A negative result of mixture saves the effort of synthesis purification andidentification of each component.
- Easy: Isolation purification and identification of active molecules from combinatorial chemistry 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 OF COMBINATORIAL CHEMISTRY:

- Efficiency is highly affected by compound size, solubility and functional group.
- Compounds produced tend to be achiral of Racemic.

- Maximum number of impurities can occur unless the reactions are very clear.
- Choosing solution phase approaches in the various stages of drug discovery and optimization have practical issues.
- The refine used is often affected by reaction types. Care must be taken so that the attachment of the reagent to the substrate and bead are unaffected. Each reaction step has to be carefully planned and often the reaction isn't available because the chemistry affects the refine.
- While the large number of compounds are created, the libraries created are often not focused enough to generate a sufficient number of hits.
- Library components whose activity exceeds a pre-defined, statistically relevant threshold, during an assay for biological activity.
- The solution phase synthesis often has purification issues related to purification procedure.

SOLUTION PHASE COMBINATORIAL CHEMISTRY:

Most ordinary synthetic chemistry takes place in solution phase. The use of solution phase techniques has been explored as an alternative to solid phase chemistry approaches for the preparation of arrays of compounds in drug discovery. Solution phase work is free from some of the constraints of solid-phase approaches but has disadvantages with respect to purification. In solution phase synthesis we use soluble Polymer as support for the product. PEG is a common vehicle which is used in solution phase synthesis it can be liquid or solid at room temperature and in solution phase synthesis it can be a liquid or solid at room temperature and show varying degrees of solubility in aqueous and organic solvent. By converting one OH group of PEG to methyl ether (MeO-PEG-OH) it is possible to attached a carboxylic acid to the free OH and use in solution phase combinatorial synthesis. Another common support which is used in solution phase synthesis is liquid Teflon consisting mainly of long of diflourocarbon groups attached to a silicon atom. When these phases are used as a soluble support for synthesis the resulting product can be easily separated from any organic solvent.

APPLICATION OF SYNTHESIS OF SOLUTION PHASE TECHNIQUE:

1. **Synthesis of Polymer by Solutions phase Combinatorial Chemistry**

A K Mishra et al., have reported the synthesis of polymer supported 1-hydroxybenzotriaxole. Reaction of the reagent with a carboxylic acid in the presence of an activating agent afforded the polymer bound activated ester which was reacted with mines to liberate the amide in solution. Supported electrophilic, nucleophilic or ionic reagents used to remove impurities from

solution have been termed scavenger reagents; polymer supported quenching reagents(PSQ) or complementary molecular reactivity or molecular recognition polymer(CMR/R polymer). Use of such reagents provides versatile counterpart to the approach. Booth and Hodges utilized their high leading amine resin derchloromethylpolystyrene and tris(2-aminoethly)ami sulphonamides. From chloromethylpolystyrene and tris (2-aminoethyl) amine in the preparation of ureas, thioureas, sulphonamides and amides[8].

2. **Synthesis of oligosaccharides and the agents antigens Involved in Cancer and**

bacterial infection

AK Mishra et al., have reported cell surface carbohydrates act as biological markers for various tumors and involved in bacterial and parasitic infections. Specific carbohydrate structures are found on particular cell populations and may be used to induce a specific immune response. These complex structures require reliable methodologies for their assembly. The Lewis antigens, a class of glycosphingolipids, are essential for cellular adhesion and recognition. In addition to their role in normal cellular adhesion processes such as inflammatory response they have been implicated in many types of cancer and bacterial infections. They develop a new synthetic route for the modular assembly of the Lewis antigens as demonstrated on the example of H- type second that lend themselves to automation. Other tumor- associated antigens including Gb3 have also been prepared. The oligosaccharides obtained from these synthesis are currently being attached to surface to enable rapid screening of carbohydrate protein interactions [8].

3. Biginelli Reaction: Polymer Supported Catalytic Approaches

Tatil et al., have reported the biginelli product, dihydropyrimidinone (DHPM) core, and its derivatives are of immense biological importance. There are several methods reported as modifications to the original biginelli reaction. Among them, many involve the use of different catalysts. Also, among the advancements that have been made to the Biginelli reaction, improvements in product yields, less hazardous reaction conditions, and simplified isolation of products from the reaction predominate. Recently, solid-phase synthetic protocols have attracted the research community for improved yields, simplified product purification, recyclability of the solid support, which forms a special economic approach for Biginelli reaction. They review role of polymer-supported catalysts in Biginelli reaction, which may involve organic, inorganic, or hybrid polymers as support for catalysts. A few of the schemes involve magnetically recoverable catalysts where work up provides green approach relative to traditional methods. Some research groups used polymer–catalyst nanocomposites and polymer-supported ionic liquids as catalyst. Solvent-free, an ultrasound or microwave-assisted Biginelli reactions with polymer- supported catalysts are also reported [16].

4. Polymer-Assisted Synthesis of Single and Fused Diketomorpholines

Kralova et al., reported the synthesis of different diketomorpholines via N-acyl- 3,4-dihydro-2H-1,4-oxazine-3-carboxylic acids is reported in this article. The key intermediates were prepared using a convenient solid-phase synthesis starting from polymer-supported Ser(tBu)-OH. After subsequent sulfonylation with 4- nitrobenzenesulfonyl chloride (4-Nos-Cl), alkylation with an α-bromoketone, cleavage of the 4-Nos group and acylation with an α-halocarboxylic acids, acid-mediated cleavage from the resin yielded dihydrooxazine-3-carboxylic acids in high crude purities. Depending on the reaction conditions, exposure to base resulted in cyclization to either oxazino[3,4-c][1,4]oxazine-diones or 3-methylidenemorpholine-2,5-diones. Further reaction with triethylsilane-trifluoroacetic acid (TES/TFA) led to olefin reduction, in the case of oxazino[3,4-c][1,4]oxazine-dione with full control of the newly formed stereocentee [17].

5. Polymer-Supported Syntheses of Heterocycles Bearing Oxazine and Thiazine

Scaffolds

Kralova et al., summarized synthetic approaches to preparing single or fused oxazine and thiazine derivatives using solid-phase synthesis (SPS). The literature survey revealed that diverse compounds bearing variously functionalized 1,2-oxazine, 1,3- oxazine, or 1,4-oxazine scaffolds and the corresponding thiazines are accessible by SPS. The latest contributions involving the stereoselective polymer-supported syntheses of morpholines indicate that the field is continuing to expand [8].

6. Rapid Synthesis of a Natural Product-Inspired Uridine Containing Library

Cheng et al., have reported the preparation of natural product-inspired nucleoside analogs using solution-phase parallel synthesis is described. The key intermediates containing alkyne and N-protected amino moieties were developed to allow for further skeleton and substituent diversity using click chemistry and urea or amide bond formation. Rapid purification was accomplished using solid-phase extraction. The obtained library comprised 80 molecules incorporating two diversity positions and one chiral center, each of which was efficiently prepared in good purity and acceptable overallyield. A bacterial morphology study was also performed [19].

7. Polymer Microarrays for the Discovery and Optimization of Robust Optical-Fiber-Based pH Sensors

Gong et al., re[prted polymer microarrays were utilized for the high-throughput screening and discovery of optimal polymeric substrates capable of trapping functional ratiometric fluorescence-based pH sensors. This led to the identification of poly(methyl methacrylate-co-2-(dimethylamino) ethyl acrylate) (PA101), which were allowed, via dip coating, the attachment of fluorescent pH sensors onto the tips of optical fibers, resulting in robust, rapid, and reproducible sensing of physiological pHs [20].

8. Aryliodoazide Synthons: A Different Approach for Diversified Synthesis of 2-Aminothiazole, 1,3-Thiazole, and 1,3-Selenazole Scaffolds

Majnooni et al., have reported several straightforward and practical processeshave been established for the construction of 2-aminothiazoles, 1,3-thiazoles and 1,3- selenazoles from aryliodoazides. Their strategies successfully proceed with a wide spectrum of substituted thioamides and its derivatives producing the resulting five- membered heterocycles obtained in satisfactory yields. The unique features of their protocols are operational simplicity and highly functional group tolerance, which make them convenient and practical routes for the preparation of various libraries of 2- aminothiazoles, 1,3-thiazoles, and 1,3-selenazoles[21].

9. Parallel Solution Phase Synthesis and Preliminary Biological Activity of a 5'-Substituted Cytidine Analog Library

Moukha–Chafiq et al., have reported 109-membered library of 5′-substituted cytidine analogs was synthesized, via funding through the NIH Roadmap Initiative and the Pilot Scale Library (PSL) Program. Reaction core compounds contained $-NH_2$ (2) and
$-COOH$ (44 and 93) groups that were coupled to a diversity of reactants in a parallel, solution phase format to produce the target library. The assorted reactants included $-NH_2$,
$-CHO$, $-SO_2Cl$, and $-COOH$ functional groups, and condensation with the intermediate core

materials 2 and 44 followed by acidic hydrolysis produced 3–91 in good yields and high purity. Linkage of the amino terminus of d-phenylalanine methyl ester to the free 5′- COOH of 44 and NaOH treatment led to core library −COOH precursor 93.In a study from libraries approach, compound 93 served as the vital building block for our unique library of dipeptidyl cytidine analogs 94–114 through amide coupling of the −COOH group with numerous commercial amines followed by acidic deprotection. Initial screening of the complete final library through the MLPCN program revealed a modest number of hits over diverse biological processes. Those hits might be considered as starting points for hit-to-lead optimization and development studies [22].

10. An Amphiphilic Polymer-Supported Strategy Enables Chemical Transformations under Anhydrous Conditions for DNA-Encoded Library Synthesis

The use of DNA-encoded libraries has emerged as a powerful hit generation technology. Combining the power of combinatorial chemistry to enumerate large compound collections with the efficiency of affinity selection in pools, the methodology makes it possible to interrogate vast chemical space against biological targets of pharmaceutical relevance. Thus, the chemical transformations employed for the synthesis of encoded libraries play a crucial role in the identification of diverse and drug- like starting points. Currently established transformations have mostly been limited to water-compatible reactions to accommodate the growing oligonucleotide tag. Herein, they describe the development of a practical catch-and-release methodology utilizing a cationic, amphiphilic PEG-based polymer to perform chemical transformations on immobilized DNA conjugates under anhydrous conditions. They demonstrate the usefulness of our APTAC (amphiphilic polymer-facilitated transformations under anhydrous conditions) approach by performing several challenging transformations on DNA-conjugated small molecules in pure organic solvents: the addition of a carbanion equivalent to a DNA-conjugated ketone in tetrahydrofuran, the synthesis of saturated heterocycles using the tin (Sn) amine protocol (SnAP) in dichloromethane, and the dual-catalytic (Ir/Ni) metallaphotoredox decarboxylative cross-coupling of carboxylic acids to DNA-conjugated aryl halides in DMSO. In addition, they demonstrate the feasibility of the latter in multititer-plate format [23].

COMPARISON BETWEEN SOLID PHASE AND SOLUTION PHASETECHNIQUE:

Parameters	Solid phase technique	Solution phase technique
1.Reagent	Large excess of reagents allowed	Optimum
2.Automation	Easy	Difficult
3.Purification	Easy	Difficult
4.Reaction	Suitable for few substances	Suitable for any organicreaction
5.Scale-up	Expensive	Easy and inexpensive

6.Dependance of reaction development	Mainly on solid support and linkers	Time

CONCLUSION:

Combinatorial chemistry continues to provide on important technique particularly to the medicinal chemist engaged in lead optimization work. Combinatorial chemistry and parallel synthesis can gently benefit by their unique features can greatly benefit by their unique features offered by new synthetic technology. These include the possibilities of high- speed parallel processing of chemical transformations in the comtext of library production, and the rapid optimization of reaction conditions. Among the solid and solution phase aynthesis solid-phase organic synthesis (SPOS) is the most important method for the production of combinatorial libraries because all the synthetic transformations successfully applied to solid phase and with the development of high-throghput screening, libraries are widerspread in pharmaceutical and agricultural chemistry

Combinatorial chemistry field has advanced rapidly over past 10 years this method has been considered as a most important advancement in medicinal chemistry and is widely exploited by pharmaceutical industries in drug discovery combinatorial chemistry can now beapplied to various new drug target development from our recent understanding of the molecular basis of disease.By considering all aspects it is understandable that this method will definitely become helpfulto mankind in development of new drugs and lead molecule at lower expenses.

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