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"COMBINATORIAL CHEMISTRY – A REVIEW"

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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. The use of combinatorial chemistry techniques has been explored as an alternative to conventional approaches for the synthesis of compounds in the drug discovery process. This technique is the starting point for the development of synthesis concepts that were intended to cover and explore the chemical space without having to prepare every individual compound. Combinatorial Chemistry technologies were developed in response to the increased screening capacities that are available when drug discovery changed its screening paradigm from a pharmacology-based approach to target oriented lead finding. This article will illustrate technique used in combinatorial chemistry, some of the advances made in recent years and their application in the synthesis of different peptides, oligosaccharides and other molecule

KEY WORDS: DNA: Deoxyribonucleic Acid , HTS: High Throughput Screening ,QSAR: Quantitative Structure Activity Relationship ,R AND D: Research And Development

INTRODUCTION

COMBINATORIAL CHEMISTRY

The relevance of high throughput, parallel method to the synthesis analysis screening and testing of materials. It relies on robotics and assisted method to generate and analyses the result. It is carried out in wells of micro titer plates. Combinatorial chemistry is a new scheme developed by academics and researchers to ease the time and cost of producing effective, marketable and competitive new drugs. Scientist make use of combinatorial chemistry to create large number of molecules that can be detected efficiently. This technique has captured the attention of many areas such as Pharmaceutical chemistry, Biotechnology and Agro chemistry. Combinatorial chemistry is a technique by which large numbers of different but structurally similar molecules are shaped rapidly and submitted for Pharmacological assay. This technique uses the same reaction conditions with the same reaction vessel to produce a large range of analogues. Nature uses a combinatorial approach to generate diverse functional macromolecules, such as the large number of antibodies that make out no self molecules. Combinatorial chemistry builds on this evolutionary approach by generating diversity in a controlled setting and then applying it to different problem such as drug innovation. Application of the combinatorial chemistry are very wide scientists use combinatorial chemistry to create large populations of molecules that can be screened capably. By producing larger, more diverse compound libraries, companies increase the likelihood that they will find novel compounds of significant therapeutic and commercial worth.

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.

Basic Concept of Combinatorial Chemistry Basic idea of this study:

Formation of number of compounds in one time

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[2]. Formation of large number of compounds which are structurally different is very important to increase the chances of finding 'hits'(active compound) and to increase the diversity of compounds and number produced in each reaction

Design of Combinatorial Chemistry

- A sequential attachment of building blocks.
- The non-sequential attachment of building blocks

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, and quantity of the compound are successively added to the preceding structure [6]

Types of Combinatorial Library

Scaffold-based Libraries

Backbone-based Libraries

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.[3]

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 1). Polystyrene is 1-2% divinyl benzene, it's particularly useful for multi-step 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 .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.[13]

Solution Phase Synthesis

Isolation of the product is the biggest challenge in this synthesis. Ion exchange resins are currently in use. These methods remove by-products and therefore eliminate the need for an aqueous work up. Fluorous phase-chemistry is another method in solution phase synthesis[25]

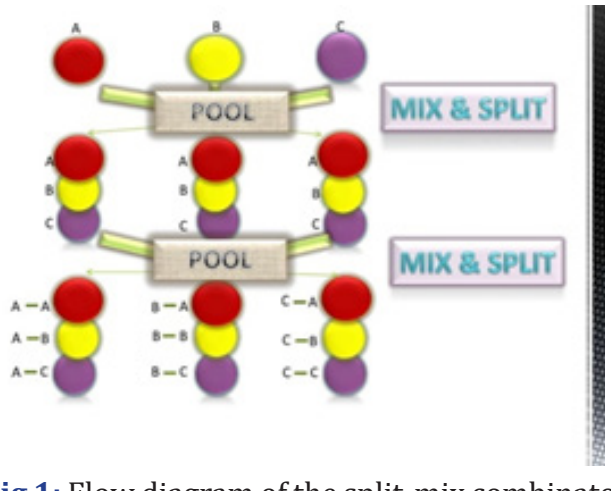

Fig 1: Flow diagram of the split-mix combinatorial synthesis

Parallel Synthesis

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.

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APPLICATIONS OF COMBINATORIAL CHEMISTRY

- Combinatorial Lead Optimization of Histamine H3 Receptor Antagonists
- Combinatorial Lead Optimization of DihydrofolateReductaseInhibitors
- Synthesis of Peptoids "Diversomers": An Approach to Nonpeptide, Non-oligomeric Chemical Diversity
- Synthesis of Peptidomimetic Inhibitors for The Hepatitis C Virus NS3 Protease
- Synthesis of Piperazinedione Combinatorial Library
- Combinatorial Lead Optimization of Neuropeptide FF Antagonists [7]

QUANTITATIVESTRUCTURE - ACTIVITY RELATIONSHIPS (QSAR)

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[14]

ADVANTAGES AND DIS-ADVANTAGES OF COMBINATORIALCHEMISTRY

Advantages

Rapid synthesis.

Richer data from screening increased likelihood of success

Broader patent protection

Disadvantages

It 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.[16]

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. 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. 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.[1]

DISCUSSION

Combinatorial chemistry and high-throughput screening techniques have fostered phenomenal growth in the amount of potentially useful pharmacological compounds. Yet, that increased number has not translated into an increase in new drug applications to and successful acceptance by the FDA . The culprit of the high attrition rate is the failure of compounds to pass toxicity testing . The intersection of predictive modelling, toxicogenomics, microscale computing, and chemoinformatics offers the possibility to mine the essential ADME (absorption, distribution, metabolism, and excretion) and pharmacokinetic data to optimize a chemical's pharmacological properties and minimize its toxicity .

The application of microscale computing for determining the metabolic fate of a compound is speeding up the drug discovery process by eliminating toxic compounds earlier in the preclinical phase of development. The Metabolizing Enzyme Toxicology Assay Chip (MetaChip) can rapidly and efficiently gauge a drug's metabolic reactions as if it were occurring in a human liver.

Although combinatorial chemistry has shown much promise for the evaluation of molecules, combinatorial chemistry is a tool, and success greatly depends on the ingenuity and intuition of the scientists. Combinatorial chemistry is a part of chemistry and its proper use and the application of intelligent design from the chemists and engineers who accomplish this are providing us with new insights into the physical world.

One challenge to preparing combinatorial libraries of inorganic materials and catalysts rapidly is trying to automate complicated,

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multistep procedures. These procedures often require choices of several chemical elements, a wide variety of supports, washing, reduction, oxidation, and calcination steps that may be difficult to carry out in a fast, automated sequence.

Perhaps one of the most challenging aspects in applying combinatorial chemistry to non-pharmaceutical chemicals is the scarcity of current methods to assay a library of inorganic materials or catalysts rapidly. Bayer, Hoechst, Ciba Specialties, and Goodrich have paid millions of dollars to form alliances with Symyx. SRI, CombiChem, and Avantium are also seeking out industrial collaboration for their combinatorial programs. UOP, DuPont, Kodak, Lucent Technologies, Dow, Celanese, and Shell reportedly are beginning in-house programs. These major chemical companies appear to have concluded that, although there may be unknowns in the current ability to synthesize and evaluate large nonpharmaceutical libraries, there are no intrinsic reasons why the success in life sciences cannot be duplicated.

CONCLUSION

The last five years has seen an explosion in the exploration and adoption of combinatorial techniques. Two decade ago, the market for pharmaceuticals was growing at around 10% per annum, but more recently, rate of the market growth has declined. The belief that combinatorial chemistry will allow the productive and cost-efficient generation of both compounds and drug molecules has fuelled enormous investment in this area. This technique has definitely decreased the cost involved in new drug research and increased the chances of finding new lead molecules. Combinatorial chemistry represents a broad spectrum of techniques that are rapidly becoming a standard part of the medicinal chemist's tool kit. The development of combinatorial chemistry is timely and undoubtedly will contribute to the discovery of new drugs that can benefit mankind. Among the solid and solution phase synthesis 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-throughput screening, libraries are widespread in pharmaceutical and agricultural field.

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