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Combinatorial Chemistry: A review

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ABSTRACT

Combinatorial chemistry is a new technique which have been used for synthesis of defined compounds having screened for pharmacological activity. This technique leads to synthesis of pharmacologically, biologically active compounds and their QSAR studies.This article emphasizes the different methods of combinatorial chemistry concept and their methodology.

Keywords: Iterative deconvolution, Positional scanning, High throughput screening.

INTRODUCTION

Elegant as the statistical techniques, a large numbers of compounds being synthesized by traditional synthetic &biological testing method. These methods are very costly. This led to the new technique called "Combinatorial Chemistry". In the combinatorial chemistry technique, there are more chemical moieties have been used and they are reacted with a parent or base molecule in a small number of defined synthetic steps. As the number of different substituents is considered, literally more than 10000 compounds are possible. Remember that the medicinal chemist can select subsets of substituents that vary in lipophilicity, steric bulk, induction, and resonance effects & use the four rules for placing & use of the substituents[1]. If this process is properly done , a relatively small number of compounds will be obtained that show the dual importance of each of the physiochemical parameters being evaluated at each position on the molecule and the effect of specific moieties at each position. This "rational" approach to drug design assumes that there is some understanding of the target receptor & that there is a lead molecule, commonly called the prototype molecule.(ex) Dihydrofolate reductase inhibitor[2] (Methotrexate), which has been one of the prototypes that laboratories have used to synthesize & test new inhibitors. Another example is Benzodiazepine which has a defined structure whose activity varies with the substituents. By the synthesis of penicillin, one fact come true that the microbial organisms produced "Antibiotics". From this it had been started screening of microbial products, looking for new antibiotics. As the same, thousands of synthetic compounds & plant extracts have been screened for anti-cancer activity. Some have called this "Irrational" drug design, but it has produced most of the drugs currently prescribed. This approach is also very expensive, particularly when one realizes the cost to synthesize, isolate & test each new compound plus the time & expense necessary to take an active compound through efficacy &safety testing before its release to the general public is approved by Govt.regulatory agencies.Combinatorial Chemistry is one method of reducing the cost of the drug discovery in which the goal is to find new leads or prototype compounds or to optimize and refine the structure activity relationships (SAR).After synthesis of new compounds by the use of combinatorial chemistry, the synthesized compounds to be tested biologically. Biological testing[3] can also be automated, in a process called "High-throughput screening", which can test tens to hundreds of structures at a time .Combinatorial Chemistry is a latest technique of synthesizing compounds, by which there is decrease in cost allotted for synthesize, isolate & testing of each compounds. In combinatorial chemistry, process called deconvulution,the synthesis is repeated in an iterative manner, producing smaller & combined mixtures of compounds. The biological screening is repeated until the active compounds are identified.

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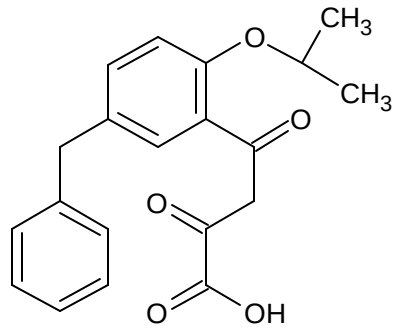
Methods used in Combinatorial Chemistry[4]:

1.One bead one compound strategy (Spatially addressable synthesis)
2.Iterative deconvulution
3.Subtractive deconvulution.
4.Bogus coin detection
5.Orthogonal pooling
6.Positional scanning.

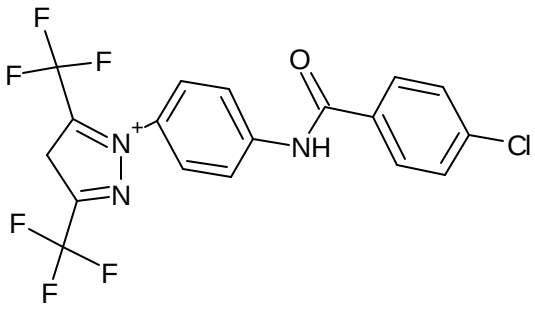
1. **One bead one compound technique[5]:**

With this strategy , a specific quantity of beads is allocated for each possible structure in the library; those beads contain only molecules of the given library member. The beads may be tagged in various ways to help identify the synthetic compound. The advan-

tage of the one bead one compound strategy is the simplicity of analysis & screening. The disadvantage is keeping the beads separate & having to deal with a large number of synthesis in parallel. It is otherwise called as Split & Mix technique.



4-(5-benzyl-2-isopropoxyphenyl)-2,4-dioxobutanoic acid



1-{4-[(4-chlorobenzoyl)amino]phenyl}-3,5-bis(trifluoromethyl)-4*H*-pyrazol-1-ium

2. Iterative deconvulution[6]:

This is the strategy first described 20 yrs ago when combinatorial chemistry was started. Each group has beads bearing a variety of compounds, but a given structure only appears in one of the groups. Suppose the active structure is ABC in the 3rd group. Since it is in the 3rd group, we know a C in position 3 is needed for activity. We synthesize a smaller library of the structures, in 3 groups.

(AAC+BAC+CAC, ABC+BBC+CBC, &ACC+BCC+CCC.)

Now when we screen those mixtures, we find activity in the middle group of beads. This tells us that a B in position 2 is required for activity. The final step is to synthesize ABC,BBC,& CBC,keeping them separate, & screen each to find ABC as the active structure.

3. Subtractive deconvulution[7]:

This is the strategy similar to iterative deconvulution but uses negative logic, namely, leave out a functional group, & if activity is absent, the functional group that is missing must be needed for activity. This is particularly useful for QSAR-type studies in which, say, a cl group is placed at several positions on a phenyl ring. The entire library is screened as a mixture to get the baseline activity level. If activity is detected, a set of sub libraries is prepared, with each missing one building block (subtraction of a functional groups from the active compounds) will be less active than the parent library. The Least active sub libraries identify the most important functional groups. A reduced library containing only these functional groups is then prepared, and the most active compounds are identified by either one compound synthesis or iterative deconvulution.

4. Bogus-coin detection[8]:

This begins with generating & screening the entire library as a single mixture. If activity is detected, the building blocks are divided into 3 groups (alpha, beta, gamma)& additional sub libraries are prepared. In these subsets, the number of building blocks from the alpha group is decreased, the number from the beta group is increased, & the number from the gamma group is unchanged. The resulting effect on activity (up.down, unchanged) suggests which group of building blocks was contributing most to activity. This approach is applied iteratively to zoom in one of the groups that are most active.

5. Orthogonal pooling[9]:

The orthogonal pooling means perpendicular or uncorrelated. In this type of pooling, we distribute the functional groups to be considered into sets of libraries A,B,C etc.,which can contain mixtures of the same compounds. However, the functional groups are distributed such that any subset in A,B shares only one functional group, For example, if we have a very small library of structures aa,ab& ac .We might put aa & ab into group A,aa & ac into group B,ab & ac into group C. If ab is the active structure, screening A,B,C would show activity in A &C , but not in B, telling us that ab is the active one.

6. Positional scanning[10]:

This is a noninterative deconvulution screening strategy in which a subset library is created with a single building block fixed at one position & all building blocks in the other positions. In principle, by selecting the functional group from the most active subset at each position, the most active compound overall is discovered. This ig-

nores interaction between building blocks, which may complicate the results.

Methods of detection, purification & analysis[11]:

1. Chromatography
2. IR
3. NMR
4. UV
5. SFC.
6. HPLC
7. Combination of HPLC-NMR technique.
8. MS.

The above methods are described in the concept **"Molecular Modeling[12]."**

The process of designing the molecule on the basis of an estimated fit onto a receptor or have similar spatial characteristics found in the prototypical lead compound. This process of designing the molecule is known as Molecular modeling.The detection, purification, analysis can be done on the above said process is mainly by the above mentioned analytical methods.This can be done mainly by the help of computer and so that it is otherwise called as Computer-Aided Drug Design.

Methods of biological screening[13]:

1. High throughput screening (HTS)
2. Virtual Screening (In silico screening)

High throughput screening[14]:

It is a broad topic, encompassing enzymes, organelles, cells, various tissues, whole animal testing via cassette dosing.

Successful HTS, programs integrate several activities, include target identification (genomics & molecular biology groups). Reagent preparation (protein expression & purification groups), compound management (information management group), assay development (biologist & pharmacologist), & high throughput library screening (biologists & chemists). Formerly, these activities were handled separately & multiple hand offs of samples were involved. It is becoming more common to integrate the activities & share expertise. This increase efficiency of the screening process. Another route to increase efficiency is a move to higher density screening platforms.Much HTS involves screening compounds that are part of the corporate store house of compounds synthesized in the past, or they may be a library purchased from a vendor.The methods for detection in HTS fall into the categories of non radiometric & radiometric.Non radiometric includes absorbance, fluorescence & luminescence spectroscopy. Enzyme assays are of a common example. Radiometric includes filtration & scintillation proximity assay (SPA).Assays use radioisotopes, so safe storage & handling are of concern.

SPA- It is a newer simple method. With the same radioactive substrate which may not necessarily need a capture group.

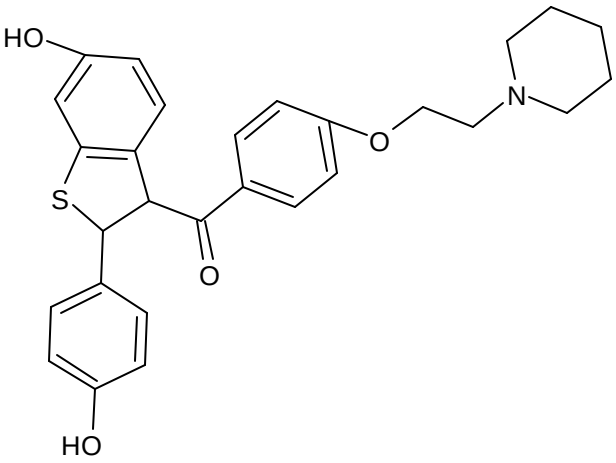
Advantages:

Over filtration method SPA is that no filtering of the solution is needed, so beads can be added directly to the assay mixture in wells or test tubes.In HTS assay use of microorganisms such as bacteria, yeast, the cloning and expression of mammalian receptors in microorganisms, probing protein-protein interactions, & very importantly, DNA & Protein arrays.

Virtual Screening[15]:

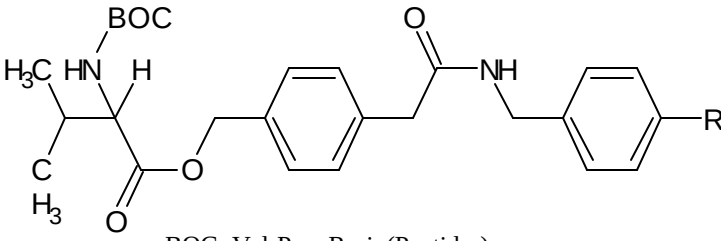
It refers to the use of computers to predict whether a compound will show desired properties or activity on the basis of its (2D) or (3D) chemical structure or its physicochemical properties. The motivation for using virtual screening arises from the flood of new structures coming from combinatorial chemistry, the expense & time required to run conventional HTS, is less in the virtual screening programs in combinatorial chemistry.Because, virtual screening method of synthesizing compounds is mainly done on the basis of 3D and 2D.But, it has not been done in HTS method. This is the further advanced program as the method of synthesizing compounds.

Example of Pharmacologically active compound

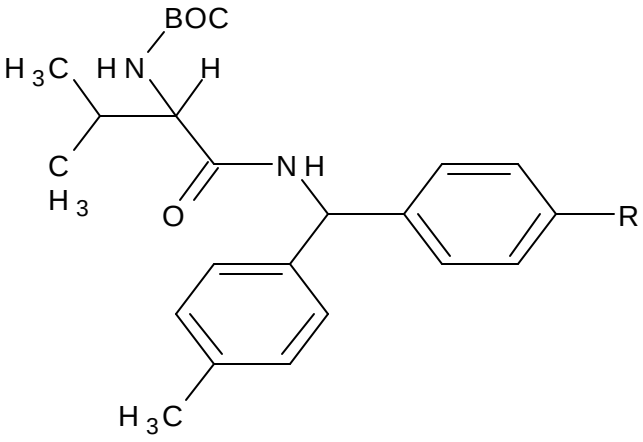


Raloxifen

Examples of Combinatorial Chemicals Synthesized by **"Combinatorial Chemistry"**



BOC- Val-Pam Resin(Peptides)



BOC- Val-MBHA-Resin(Peptides)

NOTE:
MBHA-4-Methylbenzhydramine
PAM-Phenylacetamidomethyl.

CONCLUSION:

At last Chemists and the pharmaceutical firms have a big stake in combinatorial chemistry. By the use of combinatorial chemistry, we can find more uses and applications in the pharmaceutical fields by doing the synthesis of biologically, pharmacologically & physiochemically active compounds and it has been correlated with the QSAR (quantitative structural activity relationship) parameters.

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