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Research Paper

"A REVIEW ARTICLE ON COMBINATORIAL CHEMISTRY AND IT'S DIFFERENT TECHNIQUES"

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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, nuclear receptors, synthesizer technology, parallel synthesis.

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]

1. The goal of combinatorial chemistry able to synthesize purity, chemically analyse and biologically test all the structures in the library, using few synthetic experiments as possible.
2. 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 (EotvosLorand 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] It is a young science, having only been around approximate 40 years. 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,

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Vol.11, Iss.12, Dec-2022

UGC CARE Listed (Group -I) Journal

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 this technology 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 or pressure	Possible to use	Avoided
3. Use of highly caustic reagent	Possible to use	Avoided
4. Use of inert atmosphere	Possible to use	Avoided
5. Multistep reaction	Possible to use	Avoided
6. Yield of compound	Gives single compound	Gives chemical libraries

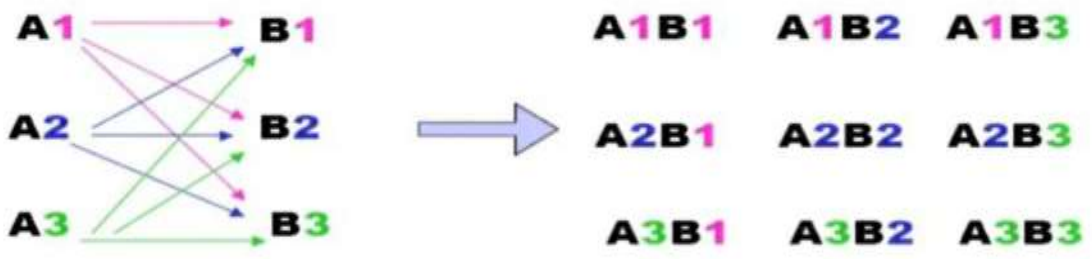
PRINCIPLE

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

1. Creating chemical libraries
2. 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

e-ISSN 2320 –7876 www.ijfans.org
Vol.11, Iss.12, Dec-2022

UGC CARE Listed (Group -I) Journal

1. Analytical techniques
2. DNA based encoding
3. Mass encoding
4. Peptide tag
5. Hard tag
6. 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:

1.Optimization
2. Identification

ADVANTAGES OF COMBINATORIAL CHEMISTRY

1. 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.
2. Economical: A negative result of mixture saves the effort of synthesis purification and identification of each component.
3. Easy: Isolation purification and identification of active molecules from combinatorial chemistry is relatively easy.
4 . 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.
5. Drug optimization: Parallel synthesis produces analogues with slight differences which is required for lead optimization

DISADVANTAGES OF COMBINATORIAL CHEMISTRY

1. Efficiency is highly affected by compound size, solubility and functional group.
2. Compounds produced tend to be achiral of Racemic.
3. Maximum number of impurities can occur unless the reactions are very clear.
4. Choosing solution phase approaches in the various stages of drug discovery and optimisation have practical issues.
5. 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 have to be carefully planned and often the reaction isn’t available because the chemistry affects the refine.

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Vol.11, Iss.12, Dec-2022

UGC CARE Listed (Group -I) Journal

6.While the large number of compounds are created, the libraries created are often not focused enough to generate a sufficient number of hits.
7. Library components whose activity exceeds a pre-defined, statistically relevant threshold, during an assay for biological activity.
8. The solution phase synthesis often has purification issues related to purification procedure.

SOLID PHASE TECHNIQUE

In solid phase combinatorial chemistry reagents or products are attached to solid supports are such as polystyrene beds- is the most traditional form of phase trafficking in solid phase organic synthesis, it's easy to purify products by filtration, it's possible to do mix and spit synthesis (a technique used to make very large libraries) excess reagents can be used to drive reactions to completion and synthesis can be automated easily.

In the basic method of solid-phase synthesis, building blocks that have two functional groups are used. One of the functional groups of the building block is usually protected by a protective group. The starting material is a bead which binds to the building block. At first, this bead is added into the solution of the protected building block and stirred. After the reaction between the bead and the protected building block is completed, the solution is removed and the bead is washed. Then the protecting group is removed and the above steps are repeated. After all steps are finished, the synthesised compound is chemically cleaved from the bead.

If a compound containing more than two kinds of building blocks is synthesised, a step is added before the deprotection of the building block bound to the bead; a functional group which is on the bead and did not reach with n added building block has to be protected by another protecting group which is not removed at the deprotective condition of the building block. Biproducts which lack the building block of this step only are prevented by this step. In addition, this step makes it easy to purify the synthesised compound after cleavage from the bead.

Advantages of solid-phase technique over solution-phase technique:

Specific reactance can be bound to specific beads.
Beads can be mixed and reacted in the same reaction vessel.
Products formed are distinctive for each bead and physically distinct.
The excess reagents can be used to drive reactions to completion.
Excess reagents and by-products are easily removed by filtration and washing.
Reaction intermediates are attached to beads and do not need to be isolated or purified.
Individual beads can be separated to isolate individual products.
Polymeric support can be regenerated and reused after cleaving the product.
Automation is possible.

Essential requirements for solid-phase technique:

A resin bed or a functionalized surface to act as a solid support.
Anchor or linker.
A bond linking the substrate to the linker. The bond must be stable to the reaction conditions used in the synthesis.
A means of cleaving the product from the linker at the end.
Protecting groups for functional groups not involved in the synthesis.

Solid support used in Solid phase synthesis

Most solid state Combinatorial Chemistry is conducted by using polymer heads ranging from 10 to 750 micro meters in diameter. The solid support must have the following characteristics for an efficient solid phase synthesis.

Physical stability and of the right dimensions to allow for a liquid handling and filtration;
Chemical inertness to all reagents involved in the synthesis;
An ability to swell while under reaction conditions to allow the permission of solvents and the agents to the reactive sites within the resin ;
Derivatisation with the functional groups to allow for the covalent attachment of an appropriate linker or first monomeric unit.
Compounds to be synthesized are not attached directly to the polymer molecules. They are usually attached by using a linker moiety that enables attachment in a way that can be easily reversed without

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Vol.11, Iss.12, Dec-2022

UGC CARE Listed (Group -I) Journal

destroying the molecule that is being synthesized and allow room for rotational freedom of the molecules attached to the polymer.

Types of solid that are used:

Polystyrene resins in this Poly styrene is cross linked with divinyl benzene (about 1% crossing) polystyrene dressing are suitable for nonpolar solvents.

Tenta gel resins polystyrene in which some of the phenyl groups have polythylene glycol (PEG) groups attached in the para position. The free OH groups of the PEG allow the attachment of compounds to be synthesized. PEG containing resins are suitable for using polar solvents.

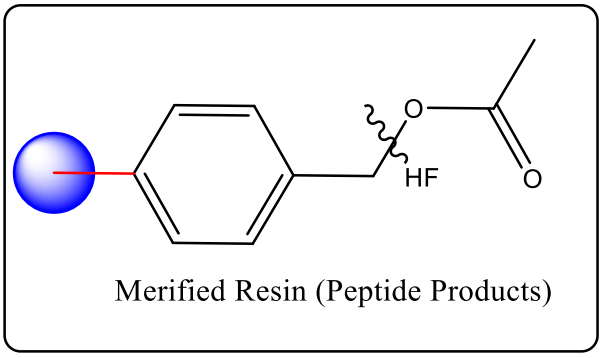
Polyacrylamide resins like super blue those swell better in polar solvents, since they contain amine bonds more closely resemble biological materials.

Glass and ceramic beads these type of solid supports are used when high temperature and high pressure reactions are carried.

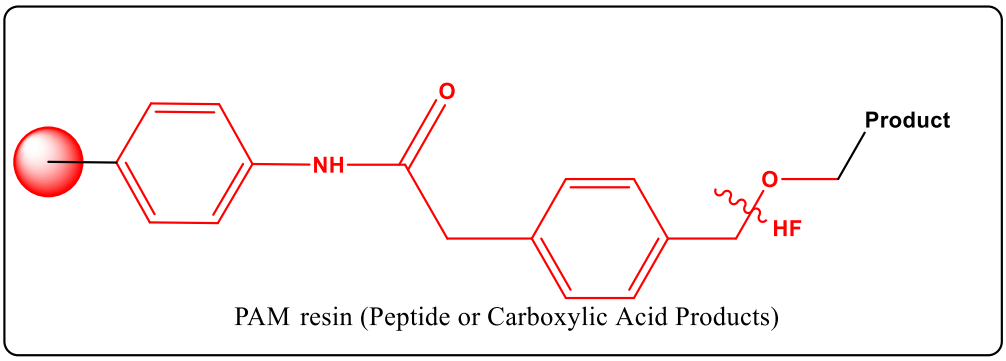
Linkers used in solid phase synthesis

To support the attachment of a synthetic target, the polymer is usually modified by equipping it with a linker. Linker must be stable under the reaction conditions, but they must be susceptible to your cleavage. Some specialized linkers have been developed to meet particular reaction or product conditions this type of linkers are known as traceless linkers, it can be cleared from the resin with no residual functionality left. These types of linkers allow the attachment of aryl and alkyl products that do not have OH or NH functionality, example of this linker include silyl group that is sensitive to acid and can be cleaved to give unsubstituted phenyl or alkyl product.

A new class of linkers was developed known as safety-catch linkers which is insert to synthetic condition and chemically transformed to allow final liberation of the product from the resin. Now ultraviolet light sensitive protecting groups are used, like affymax group is used in the synthesis of the carboxylic acid and carboxamide products.



Merified Resin (Peptide Products)



PAM resin (Peptide or Carboxylic Acid Products)

e-ISSN 2320 –7876 www.ijfans.org
Vol.11, Iss.12, Dec-2022

UGC CARE Listed (Group -I) Journal

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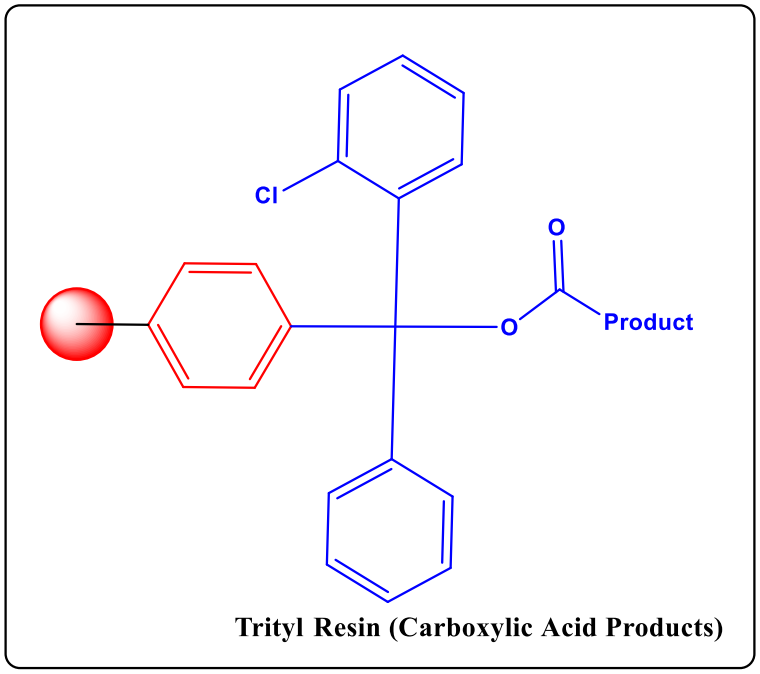


Trityl Resin (Carboxylic Acid Products)

Common protecting groups used in solid-phase synthesis and their cleavage methods.

Primary function of protecting group is to protect the portion of the molecule that is not covalently bound to the resin must be protected to avoid subsequent polymerization of excess monomers in solution non-reactive side of linkers. The protecting group must be stable to the reaction conditions of each coupling. After coupling performed, the protecting group is removed to expose a new reactive site and synthesis continues in a repetitive fashion. Cleavage conditions are dictated by the linker used.

Protecting Groups of Amine

Protecting group	**Cleavage method**
Fluorenylmethoxycarbonyl (Fmoc)	Base – catalysed (20% Piperidine in DMF)
Allyloxycarbonyl (Alloc)	Hydrogenolysis (Pd/C; water)
Benzothiazole-2-sulfonly (Bt s)	Zn-Acetic Acid Al-Hg/water

Protecting groups for Carboxylic acid

Protecting group	**Cleavage method**
t- Butyl	Acidolysis (TFA)
Dimethoxytrinyl (Dmt)	Acidolysis (Weak Acid)
Benzyloxycarbonyl (z)	Catalytic Hydrogenation Acidolysis

PARALLEL SYNTHESIS

Parallel synthesis is a method by which library construction occurs in distinct spaces on an array such that each member of the library is defined by its position of that array. Parallel synthesis leads to a discrete library by simultaneous addition of reactants in different reaction vessels and parallel handling of library sample.

Aims:

 To use a standard synthetic route to produce a range of analogues, with a different analogue in each reaction vessel, tube or well

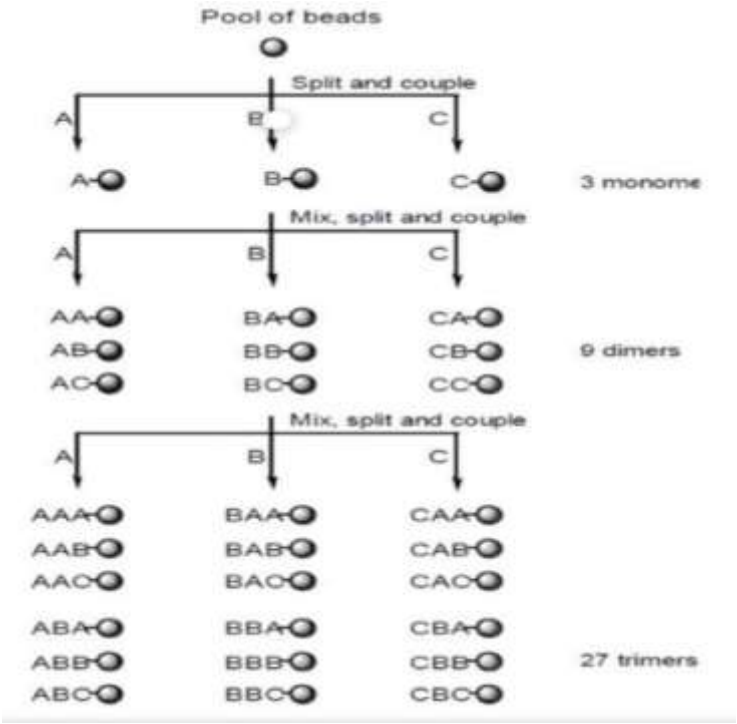
 The identity of each structure is known that is useful for producing a range of analogues for drug optimization

Houghton's Tea bag synthesis:

e-ISSN 2320 –7876 www.ijfans.org
Vol.11, Iss.12, Dec-2022

UGC CARE Listed (Group -I) Journal

Different version of parallel synthesis was developed in 1985 by Houghton for array of peptides. The beads of solid support were enclosed in permeable plastic bags, and then placed for coupling into a reaction vessel containing the solution of amino acid and the coupling reagent. All operations including removal of protecting groups, couplings washings and even the cleavages were performed on solid suppose supports enclosed in bags. All those bags which were needed the attachment of the same amino acid (eg. Alanine) were grouped together, placed into the same reaction vessel and the coupling could be done in a single operation.



Automated Parallel synthesis

Automated synthesis are available with 42,96 or 144 reaction vessels or wells
Beads or pins are used for solid support
Reactions and workups are carried out automatically
Same synthetic route used in each vessel but different reagents
Different product obtained per vessel .

Application of parallel synthesis:

1. Oxidative Cyclization Approach to Benzimidazole Libraries

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Vol.11, Iss.12, Dec-2022

UGC CARE Listed (Group -I) Journal

Eric.p.Arnold et al., have reported an efficient approach to the parallel synthesis of benzimidazoles from anilines is described library approaches to vary the N1 and C2 vectors of benzimidazoles are well established; however, C4–C7 variation has traditionally relied on 1,2-dianiline building blocks, providing limited chemical space coverage. They have developed an amidine formation/oxidative cyclization sequence that enable anilines as a diversity set for benzimidazole C4–C7 SAR generation in parallel format. The amidine annulation was achieved using PIDA or Cu-mediated oxidation to access both N–H and N–alkyl benzimidazoles. This library protocol has now been utilized for analog production in four medicinal chemistry projects. Additionally, the synthesis of aza-benzimidazoles from aminopyridines was achieved via an analogous sequence.

2. **One-Pot Parallel Synthesis of 5-(Dialkylamino) tetrazoles**

Fadych et al., have reported two protocols for the combinatorial synthesis of 5-(dialkylamino)tetrazoles were developed. The best success rate (67%) was shown by the method that used primary and secondary amines, 2,2,2-trifluoroethylthiocarbamate, and sodium azide as the starting reagents. The key steps included the formation of unsymmetrical thiourea, subsequent alkylation with 1,3-propane sultone and cyclization with azide anion. A 559-member aminotetrazole library was synthesized by this approach; the overall readily accessible (REAL) chemical space covered by the method exceeded 7 million feasible compounds.

3.Design and Solid-Phase Parallel Synthesis of 2,4,5-Trisubstituted Thiazole Derivatives via Cyclization Reaction with a Carbamimidothioate Linker

Kwon et al., have reported the preparation of 2,4,5-trisubstituted thiazole derivatives via a new solid-phase synthetic route has been conducted in this study. The synthetic route begins with the synthesis of a core skeleton 2,4-diamino(thiazol-5-yl)-substituted phenylmethanone resin obtained through a cyclization reaction with a carbamimidothioate linker. The core skeleton was substituted with diverse building blocks such as amines, alkyl halides, and acid chlorides. The products were cleaved from the solid support via a TFA/CH2Cl2 cleavage cocktail. Overall, the strategy permits the incorporation of three points of diversity into the thiazole ring system with good overall yields (Lee, T.; et al., J. Comb. Chem. 2009, 11 (2), 288−293). Finally, the library of 2,4,5-trisubstituted thiazole derivatives showed oral bioavailability through calculation of the physicochemical properties.

4. Rapid Characterization and Parameter Space Exploration of Perovskites Using an Automated Routine

Reinhardt et al., have reported hybrid, e.g., organic inorganic, perovskites from the type methylammonium lead iodide CH3NH3PbI3 are promising solar cell materials. However, due to the large parameter space spanned by the manifold combinations of divalent metals with organic cations and anions, an efficient approach is needed to rapidly test and categorize new promising materials. Herein, they developed a high throughput approach for the automated synthesis of perovskite layers with different precursor ratios at varying annealing temperatures. The layers were analyzed by optical absorption and photoluminescence (PL) spectroscopy as well as X-ray diffraction (XRD) and evaluated using two different procedures. The first one is a stepwise exclusion of nonperforming reactant ratios and synthesis conditions by using both spectroscopic techniques, followed by a final validation of the procedure by XRD. In the second procedure, only PL results were consulted in combination with high throughput screening using design of experiments (DoE) to reduce the total number of experiments needed and compared to the manual cascade approach. Noteworthy, by simple PL screening, it was possible to identify the best ratio of perovskite to byproducts and annealing temperature. Thus, only with PL, more detailed results as with the manual protocol were reached, while at the same time the effort for characterization was significantly reduced (by 60% of the experimental time). In conclusion, their approach opens a way toward fast and efficient identification of new promising materials under different reaction and process conditions.

5. Enzyme Degassing for Oxygen-Sensitive Reactions in Open Vessels of an Automated Parallel Synthesizer: RAFT Polymerizations

Wang et al., have reported an enzyme degassing method for oxygen-intolerant polymerizations was implemented in a commercially available automated parallel synthesizer and tested for reversible addition–fragmentation chain transfer (RAFT) polymerizations performed in open vessels. For this purpose, a recently reported methodology that employs the enzyme glucose oxidase (GOx) to deplete oxygen in reaction media was utilized. The effectiveness of this approach to perform unattended parallel

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Vol.11, Iss.12, Dec-2022

UGC CARE Listed (Group -I) Journal

polymerization reactions in open vessels was demonstrated by comparing experimental results to those obtained under similar experimental conditions but utilizing the common degassing method of sparging N2 to remove oxygen. The proposed experimental technique displayed good precision in performing RAFT polymerizations and good control of the obtained polymers and could be easily adapted to other systems where the removal of oxygen is mandatory. This alternative high-throughput/high-output method may have the potential to increase productivity in research projects where oxygen-intolerant reactions are involved.

MIXED COMBINATORIAL SYNTHESIS METHOD

To use 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 stretchers in each vessel are not known with certainty

Useful for finding lead compound

Capable of synthesizing large numbers of compound's quickly

Each mixture is tested for activity as the mixture

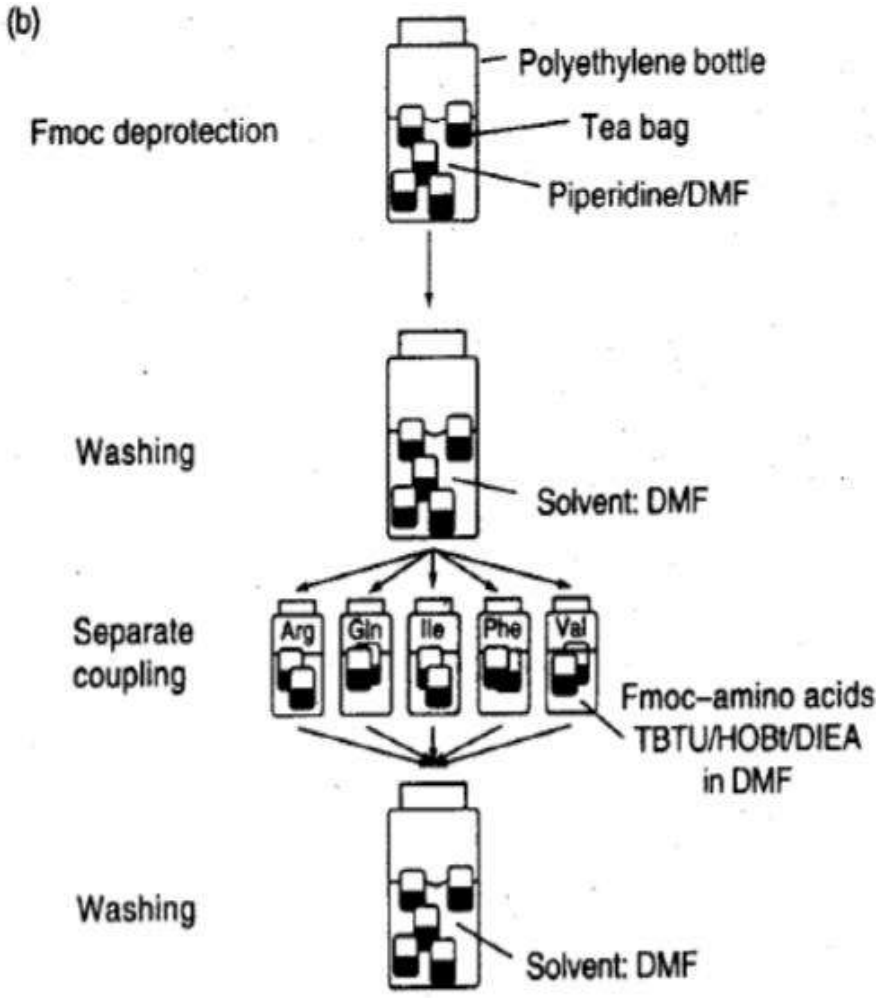
Inactive mixtures are stored in combinatorial libraries

Active mixtures are studied further to identify active component .

MIXED AND SPLIT SYNTHESIS METHOD

In this method, ingredients are assembled on the surface of beads or micro particles. In each step, beads from last step are partitioned into new building block and several groups are added. This leads to the formation of new groups, the different groups of each beads are recombined and separated once again. Process is continuous with next building block is added until the desired one has been assembled.

Example: Synthesis of all possible dipeptides from 3 different amino acid.



Application of mixed combinatorial synthesis method

e-ISSN 2320 –7876 www.ijfans.org
Vol.11, Iss.12, Dec-2022

UGC CARE Listed (Group -I) Journal

1. Combinatorial Synthesis of Binary Nanoparticles in Ionic Liquids by Cosputtering and Mixing of Elemental Nanoparticles

Neisheschein et al., have reported binary alloy nanoparticles were fabricated by two combinatorial methods: (I) cosputtering from elemental targets into the ionic liquid 1-butyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide [Bmim][(Tf)2N] and (II) by mixing elemental nanoparticles after sputtering them separately into [Bmim][(Tf)2N]. Both methods lead to the formation of Au–Cu nanoparticles (2.3 nm for cosputtered, 3.6 nm for mixed), however with different resulting compositions: cosputtered nanoparticles show a composition range of Au80–90 Cu20–10; mixing of Au- and Cu-loaded ionic liquids leads to the formation of Au75Cu25 nanoparticles. Annealing the binary nanoparticles at 100 °C shows that the mixed nanoparticles grow to sizes of 4.1 nm, whereas the cosputtered nanoparticles grow only to 3 nm.

2. Split & mix assembly of DNA libraries for ultrahigh throughput on-bead screening of functional proteins.

Lindenburg et al., have reported site-saturation libraries reduce protein screening effort in directed evolution campaigns by focusing on a limited number of rationally chosen residues. However, uneven library synthesis efficiency leads to amino acid bias, remedied at high cost by expensive custom synthesis of oligonucleotides, or through use of proprietary library synthesis platform.To address these shortcomings, they have devised a method where DNA libraries are constructed on the surface of microbeads by ligating dsDNA fragments onto growing, surface-immobilised DNA, in iterative split-and-mix cycles. This method—termed SpliMLiB for Split-and-Mix Library on Beads—was applied towards the directed evolution of an anti-IgEAffibody (ZIgE), generating a 160,000-membered, 4-site, saturation library on the surface of 8 million monoclonal beads. Deep sequencing confirmed excellent library balance (5.1% ± 0.77 per amino acid) and coverage (99.3%). As SpliMLiB beads are monoclonal, they were amenable to direct functional screening in water-in-oil emulsion droplets with cell-free expression. A FACS-based sorting of the library beads allowed recovery of hits improved in Kd over wild-type ZIgE by up to 3.5-fold, while a consensus mutant of the best hits provided a 10-fold improvement. With SpliMLiB, directed 19 evolution workflows are accelerated by integrating high-quality DNA library generation with an ultra-high throughput protein screening platform.

Application of solid phase synthesis

1. phase synthesis of Chalcones by Claisen- Schmidt Condensations

AK Mishra et al., reported that in order to accelerate the development of relatively inexpensive antimlarials that are effective aganinstchloroquine-resistant strains of Plasmodium falciparum, a methodology for the solid phase synthesis of chalcone (1,3-diphenyl-2-propen-1-one) analogues reasonably having high yield and purity. In Manual peptide synthesis vessel a mixture of 3-or-4-hydroxyacetophenone or hydroxybenzaldehyde (5 to 10 eq.),pyridine or diisopropyl ethylamine (2eq.) on our hydroxybenzaldehyde building our diisopropyl ethylamine (2 eq.) and 2-chlorotritylchloride resin (100mg,1.1-6mmol/g) in anhydrous dichloromethane(3 mL) was shaken for one hour room temperature. Resin was washed with the DMF (3x), MeOH (2x) and DCM (3x) and dried in vacuum .The resin-attached aldehydes (1eq.) or methlyketones (1eq.) were condensed with either substituted methylketones (1eq.) we're condensed with either substituted methylketones (10eq.) or substituted aldehydes (10eq.) with NaOH (0.1eq.) in 10% MeOH-DMF (3 mL total) at room temperature for 24 hours. Resins we're washed in the same sequence as the first step described above. The product was cleaved with at room temperature for 20 minute. Determination of product purity is done by HPLC.

2. The synthesis of 1,4 benzodiazepines

AK Mishra et al., have reported the choice of benzodiazepines was first inspired because of the medicinal importance of these materials and their resemblance to peptides. Here the library was constructed by a combination of three reactants. In the synthesis 1,4 benzodiazepines Fmoc is used as a common protecting group and detachment of solid support is done by tetrafluoroacetic acid.

3. Considerations for Achieving Maximized DNA Recovery in Solid-Phase DNA-Encoded Library Synthesis

Adhikari et al., have reported the DNA-encoded library (DEL) technology enables rapid, economical synthesis, and exploration of novel chemical space. Reactiondevelopment for DEL synthesis has recently

e-ISSN 2320 –7876 www.ijfans.org
Vol.11, Iss.12, Dec-2022

UGC CARE Listed (Group -I) Journal

accelerated in pace with a specific emphasis on ensuring that the reaction does not compromise the integrity of the encoding DNA. However, the factors that contribute to a reaction's "DNA compatibility" remain relatively unknown. They investigated several solid-phase reactions and encoding conditions and determined their impact on DNA compatibility. Conditions that minimized the accessibility of reactive groups on the DNA encoding tag (switching solvent, low temperature, double-stranded encoding tag) significantly improved compatibility. They showcased this approach in the multistep synthesis of an acyldepsipeptide (ADEP1) fragment, which preserved 73% of DNA for a >100-fold improvement over canonical conditions. These results are particularly encouraging in the context of multistep reaction sequences to access natural product-like scaffolds and more broadly underscore the importance of reconciling the biophysical properties and reactivity of DNA with chemistry development to yield high-quality libraries of those scaffolds.

4. Development of High-Throughput Methods for Sodium-Ion Battery Cathodes

ThamAdhikari et al., have reported the combinatorial synthesis of Li-ion batteries has proven extremely powerful in screening complex compositional spaces for next-generation materials. To date, no Na-ion counterpart exists wherein Na-ion cathodes can be synthesized in such a way to be comparable to that obtained in bulk synthesis. Herein, they develop a synthesis route wherein hundreds of milligram-scale powder samples can be made in a total time of 3 days. They focus on materials in the Na–Fe–Mn–O pseudoternary system of high immediate interest. Using a sol–gel method, developed herein, yields both phase-pure combinatorial samples of Na2/3Fe1/2Mn1/2O2 and NaFe1/2Mn1/2O2, consistent with previous reports on bulk samples of interest commercially. By contrast, the synthesis route used for Li-ion cathodes (namely coprecipitations) does not yield phase pure materials, suggesting that the sol–gel method is more effective in mixing the Na, Fe, and Mn than coprecipitation. This has important consequences for all attempts to make these materials, even in bulk. Finally, they demonstrate that these milligram-scale powder samples can be tested electrochemically in a combinatorial cell. The resulting cyclic voltammograms are in excellent agreement with those found on bulk samples in the literature. This demonstrates that the methodology developed here will be effective in characterizing the hundreds of samples needed to understand the complex ternary systems of interest and that such results will scale-up well to the gram and kilogram scale.

5. Combinatorial Synthesis of Oxysulfides in the Lanthanum–Bismuth-Copper System

M. Zhou et al., have reported establishing synthesis methods for a target material constitutes a grand challenge in materials research, which is compounded with use-inspired specifications on the format of the material. Solar photochemistry using thin film materials is a promising technology for which many complex materials are being proposed, and the present work describes application of combinatorial methods to explore the synthesis of predicted La–Bi–Cu oxysulfide photocathodes, in particular alloys of LaCuOS and BiCuOS. The variation in concentration of three cations and two anions in thin film materials, and crystallization thereof, is achieved by a combination of reactive sputtering and thermal processes including reactive annealing and rapid thermal processing. Composition and structural characterization establish composition-processing-structure relationships that highlight the breadth of processing conditions required for synthesis of LaCuOS and BiCuOS. The relative irreducibility of La oxides and limited diffusion indicate the need for high temperature processing, which conflicts with the temperature limits for mitigating evaporation of Bi and S. Collectively the results indicate that alloys of these phases will require reactive annealing protocols that are uniquely tailored to each composition, motivating advancement of dynamic processing capabilities to further automate discovery of synthesis routes.

6. Calculating Resin Functionalization in Solid-Phase Peptide Synthesis Using a Standardized Method based on Fmoc Determination

Al N Musami et al., have reported solid-phase synthesis is the method of choice for peptide preparation in both research and industrial settings. The whole synthetic process is governed by the initial functionalization of the resin. Although the literature provides several methods to determine such functionalization, the addition of an Fmoc-amino acid and the posterior spectrophotometric measurement of the dibenzofulvene adduct formed after Fmoc removal is the most widely used for this purpose. However, a range of molar extinction coefficient (ε) values and even wavelengths are currently used in the field, with no standardization of the method. Here, they propose a single-point standardization method that

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Vol.11, Iss.12, Dec-2022

UGC CARE Listed (Group -I) Journal

involves a standard 22 solution of the corresponding amino acid to be checked that is prepared freshly at the time of the analysis.

7. Solid-Phase Synthesis of RNA 5′-Azides and Their Application for Labeling, Ligation, and Cyclization Via Click Chemistry

Warminski et al., have reported RNAs with 5′ functional groups have been gaining interest as molecular probes and reporter molecules. Copper-catalyzedazide-alkyne cycloaddition is one of the most straightforward methods to access such molecules; however, RNA functionalization with azide group has been posing a synthetic challenge. They described simple and efficient protocol for azide functionalization of oligoribonucleotides 5′-end in solid-phase. An azide moiety is attached directly to the C5′-end in two steps: (i) -OH to -I conversion using methyltriphenoxyphosphonium iodide, and (ii) -I to -N3 substitution using sodium azide. The reactivity of the resulting compounds is exemplified by fluorescent labeling using both copper(I)-catalyzed (CuAAC) and strain-promoted (SPAAC) azide-alkyne cycloaddition reactions, ligation of two RNA fragments, and cyclization of short bifunctionalized oligonucleotides. The protocol makes use of oligoribonucleotides synthesized by standard phosphoramidite approach on solid support, using commercially available 2′-O-PivOM-protected monomers. Such a protection strategy eliminates the interference between the iodination reagent and silyl protecting groups (TBDMS, TOM) commonly used in RNA synthesis by phosphoramidite approach.

8. Advances in the Solid-Phase Synthesis of Pyrimidine Derivatives

Aparna et al., describes the existing synthetic approaches for the solid-phase synthesis (SPS) of differently substituted and fused pyrimidine derivatives. These synthetic strategies are classified on the basis of the different synthetic routes leading to the particular type of pyrimidine heterocycle formed. Their review discusses the application of a variety of polystyrene derived supports for the construction of pyrimidine rings. The effect of microwave heating on the solid-phase synthesis is also addressed in their review.

9. Traceless Solid-Phase Synthesis of 1'H-Spiro[Pyrrolidine-3,2'-quinazolin]-2-ones and 1'H-Spiro[Piperidine-3,2'-quinazolin]-2-ones via Lactamization of 1,2-Dihydroquinazoline-2-carboxylates

Pospisilova et al., have reported Solid-phase synthesis of 1,2-dihydroquinazoline-2-carboxylate derivatives with a quaternary carbon in position 2 and their subsequent cyclization in solution into compounds with unique 3D architectures and pharmacological relevance—spiroquinazolines, namely, 1’H-spiro[pyrrolidine-3,2′-quinazolin]-2-ones and 1’H-spiro[piperidine-3,2′-quinazolin]-2-ones. Acyclic precursors were prepared from commercially available building blocks: protected amino acids (2,4-diaminobutyric acid and ornithine), 2-nitrobenzensulfonyl chlorides and α-bromoacetophenones. The crucial step of the synthesis was a base-mediated tandem reaction including C-arylation followed by cyclization into indazole oxides, and the formation of a 5-membered heterocycle was accomplished by ring expansion into quinazolines. These derivatives were cyclized into spiro compounds in solution after cleavage from the resin.

10. Scaffolding-Induced Property Modulation of Chemical Space

Di Lorenzo et al., have reported physicochemical property switching of chemical space is of great importance for optimization of compounds, for example, for biological activity. Cyclization is a key method to control 3D and other properties. A two-step approach, which involves a multicomponent reaction followed by cyclization, is reported to achieve the transition from basic moieties to charge neutral cyclic derivatives. A series of multisubstitutedoxazolidinones, oxazinanones, and oxazepanones as well as their thio and sulfur derivatives are synthesized from readily available building blocks with mild conditions and high yields. Like a few other methods, MCR and cyclization allow for the collective transformation of a large chemical space into a related one with different properties.

11. Palladium-Catalyzed Cascade Reactions of d-Ketonitriles with Arylboronic Acids: Synthesis of Pyridines.

Yao et al., study presents the first example of the Pd-catalyzed cascade reactions of 5-oxohexanenitrile with arylboronic acids, affording important synthon 2-methylpyridines that can be further translated through C(sp3)-H functionalization to construct pyridine derivatives. Furthermore, this chemistry allows 5-oxo-5-arylpentanenitrile to react with arylboronic acids to provide unsymmetrical 2,6-diarylpyridines. Their protocol paves the way for the practical and atom economical syntheses of valuable pyridines with broad functional groups in moderate to excellent yields under mild conditions.

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UGC CARE Listed (Group -I) Journal

12. Synthesis of arylamides via Ritter-Type Cleavage of Solid-Supported Aryltriazenes

Wittert et al., have reported a novel route for the synthesis of N-arylamides via the cleavage of aryltriazenes with alkyl or aryl nitriles is presented. They developed a variation of the Ritter reaction that allows the use of acetonitrile as solvent and reagent in reactions with solid-supported precursors. The reaction was optimized for the generation of N-aryl acetamides using a diverse range of immobilized building blocks including o-, m-, and p-substituted aryltriazenes. The cleavage via the Ritter-type conversion was combined with an on-bead cross-coupling reaction of halogen-substituted aryltriazenes with pyrazoles. Additionally, the synthesis of on-bead generated arylboronic ester-substituted triazenes was shown. Their developed procedure was further expanded to use other commercially available nitriles, such as acrylonitrile, benzonitrile, and chlorinated alkyl nitriles as suitable reagents for a Ritter-type cleavage of the prepared triazene linkers.

Conclusion:

Combinatorial chemistry is a technology for creating molecules en masse and testing them rapidly for desirable properties-continues to branch out rapidly. One-molecule-at-a-time discovery strategies, many researchers see combinatorial chemistry as a better way to discover new drugs, catalysts, and materials. Compared with conventional one-molecule at-a-time discovery strategies, many researchers see combinatorial chemistry as a better way to discover new drugs, catalysts, and materials. It is a method for reacting a small number of chemicals to produce simultaneously a very large number of compounds, called libraries, which are screened to identify useful products such as drug candidates and a method in which very large numbers of chemical entities are synthesized by condensing a small number of reagents together in all combinations defined by a small set of reactions.

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