

A Subject Review on Synthetic Chemistry

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Abstract—Modern pharmaceutical innovation is supported by synthetic chemistry, which makes it possible to find, create, and produce life-saving medications and materials on a massive scale. The development of synthetic techniques and their revolutionary impact on drug discovery, industrial processes, and sustainable practices are highlighted in this overview. Traditional organic synthesis has given way to more sophisticated methods that combine automation, artificial intelligence, and reaction miniaturization. Technological advancements including flow chemistry, microreactors, biocatalysis, photoredox and electrochemical synthesis, and chemoenzymatic approaches have increased the available chemical space while enhancing scalability, efficiency, and selectivity. Furthermore, late-stage functionalization and transition-metal-catalyzed C–H activation offer strong instruments for enhancing therapeutic candidates and diversifying molecular scaffolds.

Green chemistry concepts have changed synthesis goals, placing more emphasis on waste reduction, cleaner solvents, atom economy, and renewable feedstocks, in addition to technological advancements. The emergence of green solvents, such as polyethylene glycol, water, supercritical carbon dioxide, and ionic liquids, shows how eco-friendly substitutes can be included into industrial operations. Today, metrics like the E-factor and atom economy are used to evaluate synthetic sustainability, bringing chemical innovation into line with global resource and climate issues.

All things considered, synthetic chemistry is undergoing a paradigm change as sustainability and innovation come together. Drug discovery could be accelerated while maintaining tractable synthetic routes thanks to emerging AI-driven design, automation of the design-make-test cycle, and incorporation of generative models into synthesis planning. The field is moving toward a future that strikes a balance between effectiveness, innovation, and environmental responsibility by fusing contemporary techniques with the ideas of green

chemistry, reinforcing synthetic chemistry as a fundamental component of science and medicine.

Index Terms—Artificial Intelligence, Biocatalysis, Green Chemistry, Photoredox & Electrochemical Synthesis, Synthetic chemistry.

I. INTRODUCTION

Research and development in the pharmaceutical industry heavily relies on chemical synthesis. Synthetic techniques, biocatalysis, chemo-informatics, and reaction miniaturization are some of the new technologies that are helping to improve the quality and speed of pharmaceutical research. More chemical matter that can be utilized to target more biological systems is now available thanks to new synthetic technologies, and people are realizing that advances in synthetic chemistry are fundamentally altering the process of drug discovery.¹

Over the past century, the development of novel pharmaceutical medicines by organic synthesis has significantly changed medical care, significantly lowering hospital stays, pain, and mortality. However, if this accomplishment has a negative impact on the environment, it is not flawless.²

To create molecules for small molecule drug discovery programs, the pharmaceutical industry still mostly uses synthetic chemical techniques.³

Simple techniques that provide measures for evaluating and contrasting the relative sustainability or "greenness" of synthetic procedures for active pharmaceutical ingredients (APIs) are obviously needed. Finding and outlining standards for turning down a synthetic road and beginning the hunt for a better one is the main goal of this review.⁴

Many complex compounds can now be synthesized stereo-controlled because to advancements in synthetic organic chemistry.⁵

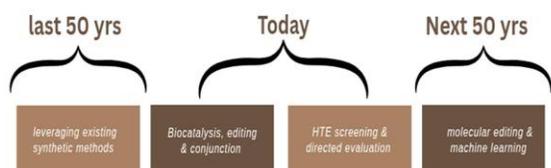


FIG NO. 1

Aristotle originally intended the phrases "organic" and "synthesis" to imply "instrumental" and "put together," respectively. This misappropriation caused misunderstanding as the definitions of the terms evolved. Since they were working with a whole blind spot about the notion of organic chemistry, the iatrochemists' preparation of numerous drug-based treatments in the 1600s is now viewed as a trial-and-error procedure. Buffon, Bergman, and Gren mistakenly restricted the definition of organic bodies to only living things as we entered the 1700s. This conceptual barrier made it impossible to identify distinct, separate organic molecules. Scheele's successful extraction of natural organic compounds and Chevreuil's accurate identification of carboxylic acids following the clumsy process of fat saponification marked the beginning of the transition in the late 1700s and early 1800s. The haze of ignorance has started to give way to organic chemistry. Before Lavoisier developed (and Berzelius improved) combustion analysis, which at last offered a trustworthy approach for comprehending the makeup of these novel chemicals, characterization techniques were crude.⁶

The transformation of nonnatural man-made organic molecules using natural catalysts, or enzymes, is not new; it has been done for over a century, either as isolated enzymes, complete cells, or cell organelles. Undoubtedly, the majority of the early research's focus was very different from what is being studied today. Therefore, the primary motivation for biochemical pathways and study a few decades ago was the clarification of enzyme processes. The tremendous potential of using natural catalysts to change non-natural chemical molecules was mostly realized in the 1980s. In synthetic organic chemistry, what began as a fad in the late 1970s may nearly be considered a fashion in the 1990s.⁷

Until recently, oligomers such as peptides, oligosaccharides, peptoids, peptide phosphates, and peptide nucleic acids, oligocarbamates, peptide vinyllogues were mostly prepared via repetitive solid-phase synthesis techniques. However, because there are only a few building blocks and synthetic methods accessible, the oligomers that are thus created have a short range of potential backbone topologies. These kinds of biologically active substances can be used as lead structures for optimization but are typically not appropriate as medicinal medicines. The goal of "combinatorial organic synthesis" is to produce low molecular weight molecules via different routes than oligomer synthesis. Ugi was the first to describe this idea in 1971. New methods for creating a variety of compounds that can then be screened to yield lead structures are provided by combinatorial synthesis. Solution-phase and solid-phase synthesis are both compatible with combinatorial chemistry. Furthermore, recent achievements in the synthesis of peptide libraries demonstrate that this method is amenable to automation. Solid-phase organic synthesis (SPOS), which has been used since the 1970s, is experiencing a rebirth as a result of these discoveries⁸

The building of molecular structures through the sequential generation of covalent bonds has been implied by the term "synthesis." To name just a few instances, the complete synthesis of complex molecular compounds like brevetoxin B, palytoxin, and calichearubicins are achievements for modern synthetic methods. However, the covalent bond's chemistry has now nearly reached its theoretical limit.⁹ Up until now, the use of enzymes in synthesis has been restricted to a few large-scale hydrolytic processes in industry and numerous small-scale material syntheses for analytical and research purposes.⁵

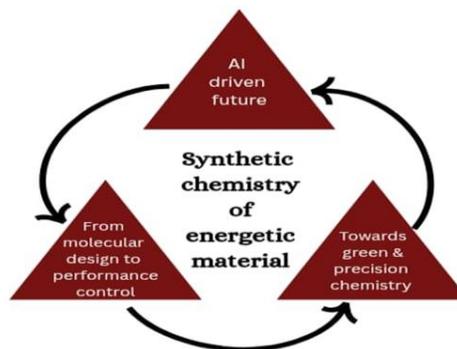


FIG NO. 2

Aim:

To demonstrate how the efficiency, selectivity, and environmental effect of synthetic processes in drug discovery, pharmaceutical research, and sustainable chemical practices with the help of automation, artificial intelligence, flow chemistry, biocatalysis, and green chemistry concepts.

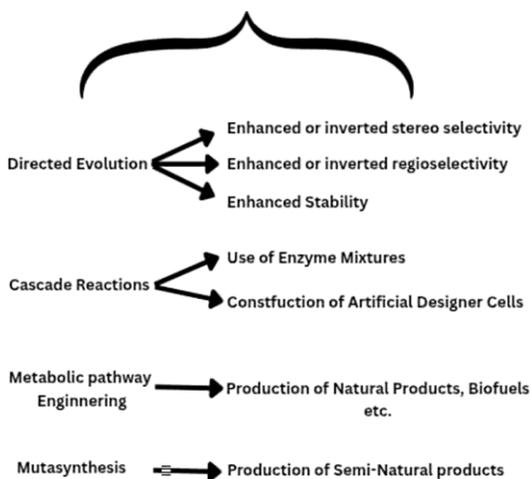
Enzymes in Organic Chemistry & Biotechnology

FIG NO. 3

Objectives:

- To investigate how cutting-edge technology like automation, artificial intelligence, and microreactors can be integrated to increase the accuracy and efficiency of synthetic processes.
- To investigate how contemporary methods like C-H activation, photo redox and electrochemical synthesis, and flow chemistry can be used in sustainable medication creation.
- To evaluate the difficulties, possibilities, and prospects for combining sustainability and creativity in synthetic chemistry.

Background:

Synthetic chemical advancements throughout the past century have made it possible to find and manufacture significant, life-altering medications, which have improved patient health all around the world. Furthermore, current advancements in biocatalysis, chemoinformatics, reaction miniaturization, and new synthetic techniques have the potential to speed up and enhance the caliber of pharmaceutical research

outputs. The creation of new educational resources that reflect scientific practice requires an understanding of the nature of science. Three categories of issues (project level, synthetic planning, and day-to-day)¹⁰

Although enzymes have been utilized for a century in organic chemistry and biotechnology, several obstacles have hindered their broad utilization, such as their frequently noted weak thermostability, limited substrate scope, and low or incorrect stereo- and/or regio-selectivity.¹¹

Reaction measurements and their correlations are explained, along with their justification for green chemistry. The notion of mass intensity makes it simple to determine the mathematical formula that compares the characteristics of a reaction sequence, including the yields of each stage, atom economy, mass of auxiliaries, and possibly their retrieval, to the reaction metrics, excess of reactants, such as the E-factor.¹²

Over the past 25 years, the impact of the second green chemistry principle that synthetic methods developed to increase the incorporation of all ingredients in the process into the end product on the core principles and manufacturing efficiency of chemicals is evaluated. It has been crucial in drawing the attention of the global chemical industry and especially the pharmaceutical industry to the issue of waste production in the production of chemicals. It sparked a paradigm change in the way organic synthesis efficiency is measured and gave rise to the development of cleaner, more sustainable technologies.¹³

Global warming, climate change, carbon emissions, and the loss of natural resources have all recently gained prominence on development agendas worldwide. Both wealthy and developing nations are worried about the negative effects of these environmental trends. In fact, there is increasing global agreement that climate change is occurring, will only worsen, is caused by humans, that experts agree, that we can take action, and that there is still hope if we act quickly.¹⁴

Rationale:

- 1) Synthetic chemistry plays an important role in making new drugs and materials, but it must also focus on green and safe methods to reduce pollution and waste during production.

- 2) This review is made to explain how modern technologies like artificial intelligence, automation, and green chemistry are changing the way chemical synthesis is done.
- 3) The study helps to understand how reactions, solvents, and processes can be improved to make drug development faster, cheaper, and more environment friendly.
- 4) It gives an idea about how new reaction methods like photo-redox, flow chemistry, and biocatalysis help in producing more effective and selective medicines.
- 5) The primary reason of this review is to show the importance of combining innovation with sustainability in chemistry for the betterment of industry, environment, and human life.

II. INNOVATIONS IN SYNTHETIC CHEMISTRY



FIG NO.4

It is feasible to pinpoint specific patterns where a great deal of research has been conducted and where notable advancements have been made when we examine the field of green chemistry from its inception as a coherent area of study, which began with the creation of environmentally friendly processes in the early 1990s.¹⁵

"Automated & AI driven synthesis"

Chemical biology, materials science, medicine development, and engineering are all based on

synthetic organic chemistry. However, carrying out intricate chemical synthesis on its own calls for specialized knowledge, which is often gained through years of study and practical laboratory experience. The creation of technology that could simplify and automate chemical synthesis has been an ongoing endeavor for fifty years. Improved processing power, data availability, and algorithms are generating renewed interest in artificial intelligence (AI), which is reversing the modest progress that was previously achieved.¹⁶

Computational organic synthesis has been a long-standing objective in organic chemistry since the creation of the first system for this purpose, LHASA. This objective has been sought by researchers because an automated system could facilitate the easier, faster, and more cost-effective discovery of new materials (such as medications, polymers, proteins, enzymes, etc.) and novel reaction pathways. Even after forty years, new advancements in the application of AI approaches appear to be highly promising, even though this ideal is still largely unfulfilled.¹⁷

Over the past few years, the discipline of computer-aided synthesis prediction (CASP) has undergone significant evolution. The area is currently dominated by machine learning (ML) based techniques, however its history dates back to Corey's groundbreaking work on rule-based systems for synthesis prediction and the synthesis planning software Logic and Heuristics Applied to Synthetic Analysis (LHASA). Since CASP has already been reviewed a number of times, we will concentrate on the main ideas and current advancements in this study, with a particular focus on using machine learning for CASP.¹⁸

Due to the very nonlinear behavior of chemical processes, producing chemicals is a hard undertaking. As a result, conventional methods may not be very efficient in planning or forecasting such processes and their best results. Finding methods to increase production and efficiency while cutting costs and time has therefore always been difficult.¹⁹

Chemists utilize retrosynthesis, a problem-solving method that iteratively converts target molecules into progressively smaller precursors, to schedule the synthesis of tiny organic compounds. Although computer-aided retrosynthesis is now slow and produces results of poor quality, it could be a useful tool. Here, we find retrosynthetic paths using symbolic artificial intelligence (AI) and Monte Carlo

tree search. In order to pre-select the most promising retrosynthetic steps, we integrated Monte Carlo tree search with a filter network and an expansion policy network to direct the search. Nearly every reaction ever reported in organic chemistry was used to train these deep neural networks.²⁰

Chemistry is one of the many scientific disciplines that heavily push artificial intelligence (AI), as is the case in other domains. AI is being studied more and more in chemical disciplines, despite the fact that chemistry has historically tended to be a conservative profession that adopts new ideas more slowly than others. Computational techniques have long been used in medicinal chemistry to help find and optimize active molecules, with the support of cheminformatics and computer-aided drug design. Numerous articles pertaining to AI are now being published in the literature that is important to medicinal chemistry, and we expect that this number will continue to rise.²¹

In drug-discovery endeavors, organic synthesis remains a rate-limiting component after decades of groundbreaking academic study. Here, we outline some of the current issues facing synthetic organic chemistry from the standpoint of the pharmaceutical sector and point out troublesome processes that, if resolved, would be widely used in the development of game-changing medications. The presence of amines, N-heterocycles, and unprotected polar groups in pharmacological compounds presents significant synthesis problems. New processes that facilitate stereoselectively substituted aliphatic heterocyclic ring synthesis, C–X or C–C bond creation, greater C–H bond activation, late-stage functionalization, and non-traditional disconnections are also required. We further stress that the use of syntheses that are compatible with biomacromolecules will grow, and that the drug-discovery process might be significantly accelerated by emerging technologies like machine-assisted techniques and artificial intelligence for synthesis planning.²²

Computer-aided synthesis planning (CASP) combines chemists' intuition with computer dependability. CASP has emerged as a crucial instrument in both academic and corporate research, serving as a bridge between the distinct creativity of humans and the unmatched computational power of computers. CASP will play a bigger role in the field of synthetic chemistry as a result of the explosion of new chemical reactions, improvements in computer performance,

and the revolution in algorithms. This will lead to the creation of new and extremely effective natural product and drug candidate syntheses.²³

The management of vast quantities of accumulated reaction examples, machine learning based on these experimental findings, and the subsequent creation of synthesis devices are the fundamental technologies of automated organic synthesis. In order to move closer to complete automation, organic synthesis must be digitized.²⁴

We must look into innovative, creative approaches that enhance our capacity to develop new medications because of the significant difficulties involved in drug discovery and the task's significance to society. Efforts to create and use a variety of computational techniques to aid in drug development have increased recently, often with outlandish promises on their importance.²⁵

The chemical universe was limited to the virtual products that could be obtained from 17 one-step reactions in order to guarantee compatibility with automated on-chip synthesis. We successfully synthesized 25 de novo designs in flow.²⁶

In drug development efforts, generative models are commonly employed for de novo design in order to suggest novel compounds. However, even though the ability to synthesize the generated molecules is a crucial prerequisite for such methods to be helpful in reality, the question of whether or not the generated molecules can be synthesized is not systematically taken into account during generation. There is currently no agreement on whether a molecule is synthesizable, despite the development of methods to evaluate its "synthesizability."²⁷

The field of drug design has seen a radical change in recent years due to the quick development of generative artificial intelligence (GenAI), which has provided creative answers that could hasten the identification of new treatments. Algorithms and models that automatically produce new data, such as text, pictures, and molecules, and frequently mimic the features of preexisting datasets are referred to as GenAI. This thorough analysis explores the subject of GenAI for drug creation, highlighting new developments and approaches that have advanced the discipline. In particular, we concentrate on three well-known paradigms that have had a particularly significant influence in recent years: transformers,

diffusion models, and reinforcement learning algorithms.²⁸

An important development in artificial intelligence (AI) is the addition of multimodal capabilities to large language models (LLMs). Specifically, the potential of these models is increased by their capacity to analyze and interpret visual data, such as intricate graphs and plots commonly found in chemistry. Multimodal AI may address a wider range of issues thanks to this combination of text and image processing, particularly in fields where visual information is essential for comprehending and resolving issues.²⁹

Artificial intelligence (AI) has gained popularity recently as a useful tool for education and learning. It has also showed promise as a problem-solving tool. ChatGPT is a technology that has drawn interest in the field of education because it uses AI to enhance teaching and learning. This study examines ChatGPT's challenges in understanding and solving chemical topics related to the Introduction to Material Science course.³⁰

One important enabling technology for environmentally friendly and sustainable chemical manufacturing is enzyme catalysis. The core of this technology, which is presently being altered by artificial intelligence (AI) techniques like machine learning, is the development of appropriate enzymes. Enzyme design and discovery were done using AI-based techniques.³¹

It takes a lot of work to get knowledge from journal articles on synthetic biology for machine learning (ML) applications. The extraction of published data about microbial performance under intricate strain engineering and bioreactor conditions can be sped up with the advent of natural language processing (NLP) technologies like GPT-4.³²

Like other scientific domains, chemistry is one of the many that heavily push artificial intelligence (AI). Despite chemistry's historical tendency toward conservatism and its slower rate of adoption of new ideas, artificial intelligence is being studied more and more in chemical sciences. In medicinal chemistry, computational techniques have long been used to help find and optimize active molecules, boosted by cheminformatics and computer-aided drug design.²¹

Photoredox & electrochemical synthesis:

The synthesis of complex organic compounds is an important and rapidly evolving field in terms of

biological applications and medications. Here, organic electrocatalysis offers a substitute for the conventional chemo-, regio-, and stereoselective synthesis techniques. By transferring electrons, electro-organic processes take place at RT and normal pressure. It has been discovered that electrocatalysis is a gentle method for creating electrophilic bases, nucleophiles, and substrates in-situ from extremely stable and low-level chemicals. This method can then be used to increase the accessibility of heterocycles.³³ It is well known that the promising features of electrochemical sensors such as the ability to gather information in real time, with minimal manipulation of the system under study, and with minimal environmental impact have led to a notable rise in research on these devices. The main characteristics, production techniques, and applications of carbon nanomaterials in the creation of electrochemical sensors for the detection of pharmaceuticals and other clinically relevant chemicals are all covered in this article. To guarantee that the medication performs its function as intended without any issues that can jeopardize the patient's health and quality of life, drug analysis is crucial for quality control in this situation. Furthermore, the indication of successful diagnoses depends critically on analytical techniques that may identify substances of therapeutic importance in biological fluids.³⁴

In the last ten years, photoredox catalysis has become a key tool in synthetic organic chemistry for the selective activation of tiny molecules and the creation of chemical bonds. Photosensitizers can use this state-of-the-art platform to transform visible light into chemical energy, which causes the production of intermediate reactive radicals.³⁵

With the introduction of photoredox catalysis, numerous new reactions have been accomplished and new synthetic paradigms have been developed. However, there are a number of problems with contemporary photoredox chemistry, including inadequacies in scalability and reaction efficiency. Moreover, it is common practice to use light wavelengths that are greater than the energy needed for a chemical reaction.³⁶

The chemical industry has taken notice of all these characteristics and has acknowledged the potential of photoredox techniques to accomplish effective and long-lasting catalysis. For instance, photoredox catalysis has been employed by the pharmaceutical

industry in a number of synthetic transformations that are essential to the research and discovery of new drugs. Protocols for the direct and specific functionalization of drug-like scaffolds, such as perfluoroalkylation, halogenation, amination, and alkylation, are one example. Using non-toxic and easily accessible materials, photoredox techniques have been employed to install such minor functions in order to directly affect the ADME-tox (absorption, distribution, metabolism, excretion, and toxicology) characteristics of a lead candidate.³⁷

Photoredox catalysts, which capture the energy from the absorption of low-energy light in the visible spectrum, have recently been employed by synthetic chemists as efficient instruments to start a variety of organic transformations. Particularly in recent years, the development of methods based on the single electron transfer capabilities of photoredox catalysts has caused a paradigm change in how synthetic chemists see both photochemistry and redox modifications of organic molecules.³⁸

III. FLOW CHEMISTRY & MICROREACTERS

Over the past ten years, laboratory-scale flow-through processes have rapidly advanced and are now a key technique for increasing synthetic efficiency through process optimization & automation. In practice, flow devices serve as a vital conduit between process engineers and bench chemists. The current analysis concentrates on two distinct areas of contemporary flow chemistry where significant benefits over the related batch techniques have emerged. One of the many enabling technologies, flow chemistry, is best paired with other enabling technologies, including energy input. Heat can be used to accomplish this and produce supercritical conditions.³⁹

When used to conduct hazardous or challenging chemical reactions, flow synthesis has numerous benefits. Continuous production also makes it possible to scale up reactions quickly without requiring major route reconstruction. Crucially, it can also offer a flexible framework for constructing integrated multi-step reactions, resulting in more sophisticated chemical structures. A situation of smooth connection between successive steps of a longer chemical sequence is produced by the development of multifunctional micro and meso-flow

systems that make use of in-line purification and diagnostic capabilities.⁴⁰

The preparation of fine molecules, such as natural products or (APIs), using flow technology has been increasingly popular recently. Even if the pharmaceutical industry still uses multipurpose batch reactors, it is evident that interest in continuous flow synthesis of organic compounds, especially highly functionalised and chiral chemicals, is developing. Continuous flow synthetic approaches can be easily integrated with other supporting technologies such as microwave irradiation, supported reagents or catalysts, photochemistry, innovative solvent systems, 3D printing, inductive heating, electrochemistry or microreactor technology. This combination may enable the development of completely automated, often more sustainable, and efficient operations. Additionally, it has been demonstrated that continuous flow conditions can lead to a safer manufacturing method for organic intermediates and APIs, minimising the danger of carrying out some synthetic procedures that were previously forbidden due to safety concerns.⁴¹

Controlling the reaction conditions and chemical reactivity is necessary for the synthesis of complex compounds. Although most chemical discovery is driven by reactivity, improvements in reaction condition control have sped up development and discovery. Flow reactors and automated synthesizers are examples of recent instruments. In this Synopsis, we outline how our groups' chemical progress in single-stage reactions, materials synthesis, and multistep processes has been made possible by flow reactors.⁴²

A wide range of chemical processes that might otherwise be challenging or ineffective are made possible by the intrinsic qualities of flow chemistry, a method that has been thoroughly investigated. A flow chemistry module is essentially a stable set of conditions that reagents are subjected to. Usually, these conditions are thought of as an activation or control mechanism that is forced from the outside, like heat or light. We anticipated that the primary advantages of the technique reproducibility and the correlation between reaction time and reactor position would enhance the teaching and spread of this field. Because of these advantages, a flow module could be redefined to be more synthetically relevant depending on the total produced effect. By classifying flow

modules into two subclasses generators and transformers we suggest rethinking the approach to flow modules. Each of these subclasses can be characterised as a collection of specifications for executing a certain transformation or generating a reactive intermediate.⁴³

Continuous flow processing, a key technique, has changed chemistry and enhanced our synthetic capabilities. As a result, many new techniques have been created to more efficiently and consistently create pharmaceutical compounds that are commercially viable. This review article will illustrate the holistic systems approach and various applications of flow chemistry to the preparation of pharmaceutically active molecules in order to demonstrate the value of this approach in all areas, from synthesis, in-line analysis, and purification to final formulation and tableting.⁴⁴

Complex chemical structures, long synthetic routes, laborious workup methods, and a significant environmental impact are some of the ongoing hurdles facing the complete synthesis of natural goods. Over the past 20 years, it has been demonstrated that using various types of microreactors to carry out chemical transformations in continuous flow is effective in terms of increased reaction yield and selectivity, outstanding reproducibility, simple scale-up. Additionally, the rapid synthesis of natural products—which has been made possible in continuous flow based on the significant improvement of overall yield within a short residence time via processing intensification and systematic automation—is important to supply sufficient quantity for the bioactivity investigation of structural diversity modification, structure-activity relationship during drug discovery, and the growing consumption of medical treatment.⁴⁵

Over the past ten years, microchemical systems with a wide range of chemistry applications have rapidly evolved. These systems provide a better knowledge of the underlying pathways and kinetics while also facilitating the development of synthetic approaches.⁴⁶

Biocatalysis and chemoenzymatic synthesis

In the pharmaceutical industries as well as in academia, biocatalysis has emerged as a significant component of contemporary organic synthesis. Its success has mostly been attributed to the quick expansion of the chemical processes that can be accessed, which is made feasible by high-throughput

laboratory evolution techniques for biocatalyst optimization and sophisticated tools for enzyme discovery. A long range of bespoke enzymes with high efficiencies and selectivities can now be produced quickly and on a g to kg scale. This covers the most current developments in the field's methodology, including route design, enzyme discovery, protein engineering, and the use of biocatalysis in industry.⁴⁷

Biocatalysis has numerous applications across numerous industries as a substitute for chemical catalysis. The most well-known examples concern the utilization of enzymes in organic synthesis, specifically in the manufacturing of chiral compounds for the flavour and fragrance and pharmaceutical sectors. Moreover, biocatalysts are frequently used in the manufacturing of speciality and bulk chemicals.⁴⁸ Biocatalysis has become a popular method in organic synthesis, which is also widely utilised in industry, by using certain enzymes for organic transformations. Many biotransformations have remarkable stereo-, regio-, and chemoselectivity as well as generally high activity due to precise control of the reaction in the biocatalyst's active zone. This control is influenced by specific activating contacts between the reagents and the protein, minute movements of the catalyst, and the exact positioning of the chemicals in respect to one another in a carefully calibrated three-dimensional environment. The catalyst can be modified to fit the intended reaction and process through the use of enzyme engineering. For a variety of reactions, a fully stocked biocatalytic toolbox is prepared for usage. One can experiment with the many possibilities for generating unique transformations and so opening new, brief paths to desired target molecules by providing nonnatural reagents and settings as well as developing biocatalysts. The efficiency of biocatalysis is further increased by combining many biocatalysts in a single pot to carry out multiple reactions at once.⁴⁹

For many pharmaceutical medicines to be safe and effective, chirality is essential. In the pharmaceutical business, the manufacturing of pharmacological intermediates in single enantiomers has grown in significance. Microbes and the enzymes they produce have a significant capacity to alter synthetic substances with high chemo-, regio-, and enantioselectivities. The enzymatic method is now very effective and commercially feasible because to recent developments in directed evolution that allow mutants

to be tested under process conditions to increase biocatalyst activity and selectivity.⁵⁰

Biocatalysis has emerged as a key technology in the commercial production of bulk chemicals, pharmaceutical and agrochemical intermediates, active medications, and food components. However, biocatalysts' perceived or real limitations, such as their restricted substrate range, operating stability, and enzyme availability, may be partially to blame for the small number and variety of applications. Recent developments in genomics, directed enzyme evolution, and biodiversity exploitation should address these limitations.⁵¹

Biocatalysis is increasingly being used to produce enantiomerically pure compounds for usage as pharmaceutical intermediates. Advances in genomics, screening, and evolution technologies have led to an increase in the availability of new and dependable biocatalysts appropriate for industrial-scale use. This is fueled by a growing need for catalysts that can handle the increasingly complex active pharmaceutical ingredients. Enantioselective ketone reductions and enantiospecific hydrolyses continue to be the foundation of the great majority of biotransformation processes used to produce optically active pharmacological intermediates.⁵²

Over the last century, biocatalysis has advanced dramatically. Exploration of natural enzymatic processes is ongoing, aided by the integration of multidisciplinary technology. Robust biocatalysts that are extensively employed in industrial production are the result of protein engineering.⁵³

Biocatalysis's application in industrial synthetic chemistry is poised for substantial expansion. Enzymes and biocatalytically active cells may now selectively and effectively modify apolar chemical molecules as well as water-soluble substances through the use of biocatalytic processes in both organic solvents and watery environments. Many chemical companies have started to greatly expand the quantity and complexity of biocatalytic processes they use in their synthesis operations as the use of biocatalysis for commercial chemical synthesis becomes more accessible.⁵⁴

Due to the growing demand for more environmentally friendly chemistry, enzymatic catalysis is currently being utilized extensively in the pharmaceutical business and is rapidly spreading into the fine and specialty chemicals sector. In order to meet the

demand for scalable and cost-effective processes that are prepared for direct industrial adoption, this analysis emphasizes the growing emphasis on improving process performance measures.⁵⁵

Biocatalysis's role and strength in sustainable chemistry have been steadily advanced to their current exceptional level. Many notable advances in biology, chemistry, and engineering have demonstrated the problem-solving potential of biocatalysis. The application of biocatalytic synthesis in contemporary chemistry has undoubtedly been expedited by developments and achievements in the biological sciences as well as multidisciplinary collaboration with chemistry. Sustainable chemistry and customer-centric value creation in the pharmaceutical, food, taste, fragrance, vitamin, agrochemical, polymer, specialty, and fine chemical industries have already benefited greatly from resource-efficient biocatalytic manufacturing techniques. Biocatalysis has the potential to significantly impact not only industrial processes but also the development of entirely new value-creation chains.⁵⁶

Both chemoenzymatic and biocatalytic biosynthesis are potent organic chemistry techniques that employ enzymes to carry out specific reactions and enable the effective synthesis of organic molecules. These methods have the advantages of working with complicated substrates, gentle reaction conditions, and good selectivity. Chemoenzymatic techniques for the synthesis of complicated compounds have become increasingly popular in the field of organic chemistry. According to this paradigm, modern synthetic methods and biocatalytic technologies collaborate in a multi-step process to reach a target molecule. Chemoenzymatic methods have the potential to simplify access to important bioactive compounds due to the remarkable regio- and stereoselectivity of enzymatic transformations and the variety of reactions in contemporary organic chemistry.⁵⁷

C-H activation and late stage functionalization

A growingly potent platform for chemical synthesis, transition metal-catalyzed C-H activation has applications in the pharmaceutical, material sciences, late-stage modification, and natural product synthesis sectors, among other fields.⁵⁸

Since the "12 Principles of Green Chemistry" were established more than 20 years ago, chemists have become increasingly aware of the need to protect the environment and conserve natural resources by

employing synthetic pathways and materials sparingly. Theoretically, direct activation and functionalisation of C-H bonds is more economical than installing intermediary functional groups. Large-scale applications are still unsustainable, nevertheless, due to a number of problems. In this Outlook, we emphasise the research areas that seek to address the sustainability concerns of C-H activation, including the replacement of metal oxidants, the avoidance of static directing groups, the introduction of bioderived solvents, and the pursuit of abundant metal catalysts.⁵⁹ Any of a variety of methods can be used for CH activation, most frequently involving catalysts that cleave an organic compound's carbon to hydrogen covalent link and replace the hydrogen atom with a functional group. In organic chemistry, CH activation for functionalization is the cutting edge. It allows chemists to conduct processes with the least amount of byproduct pollution and in the most ecologically friendly way possible.⁶⁰

The selective conversion of common but inert C-H bonds to other functional groups has wide practical implications, ranging from more efficient techniques for fine chemical synthesis to the replacement of current petrochemical feedstocks with less expensive and more accessible alkanes. Over the past 20 years, there have been many cases of C-H bond activation at transition-metal centres, often with exceptional selectivity and under relatively benign conditions. Our knowledge of how these organometallic reactions work, as well as their inherent benefits and limitations for practical alkane conversion, has advanced significantly, despite the lack of profitable practical applications. Actually, the emergence of promising catalytic systems in recent years shows how organometallic chemistry can be used to produce practical C-H bond activation techniques that will eventually enable us to more effectively and cleanly utilize Earth's alkane resources.⁶¹

The number of studies detailing synthetic techniques that make use of catalytic sp³ and sp² C-H bond activation has increased exponentially in recent years. Many have become effective synthetic methods for obtaining motifs that are physiologically active. In fact, application to the production of C-C and C-heteroatom bonds offers fresh guidelines for the development of novel pharmacological substances. The usefulness of these transformations in medicinal

chemistry is demonstrated here by a few recent new C-H activation methods.⁶²

The rapidly developing subject of organic electronics is largely dependent on the synthesis of π -conjugated molecules and polymers. Classic aryl cross-coupling methods such as the Stille and Suzuki have been used extensively in the production of π -conjugated molecules and polymers. However, creating the intermediates needed for conventional cross-couplings may require a number of steps and the use of harmful and dangerous substances.⁶³

In the last stages of synthesis, late-stage functionalization (LSF) can add significant chemical groups. LSF could significantly influence drug discovery and expedite the creation of varied chemical libraries and novel chemical entities. Without the requirement for time-consuming de novo chemical synthesis, functional group tolerance and moderate conditions provide access to novel compounds that are difficult to obtain using traditional methods.⁶⁴

Late-stage functionalization (LSF) techniques have significantly changed the chemical synthesis environment in the last ten years. In particular, C-H functionalization techniques increase resource economy while paving the way for new retrosynthetic disconnections. Medicinal chemists are now able to include LSF tactics into their drug discovery programs thanks to the effective application of a number of novel methodologies to the C-H diversification of medicines. This review demonstrates how the application of these contemporary techniques enables greater efficiency in the drug discovery process and emphasizes the noteworthy advancements made in the late-stage C-H functionalization of medicines and drug-like molecules.⁶⁵

IV. CHALLENGES AND OPPORTUNITIES

- Our definition of late-stage functionalisation (LSF) clarifies the term's prior ambiguity and should assist chemists in determining whether a reaction qualifies as LSF.
- While site selectivity is an optional but frequently sought attribute, chemoselectivity is a prerequisite for LSF reactions.
- Small-molecule catalysts or reagents are used in many LSF processes. To solve unresolved selectivity issues for the creation of novel LSF

reactions, complementary strategies are thought to be required.⁶⁶

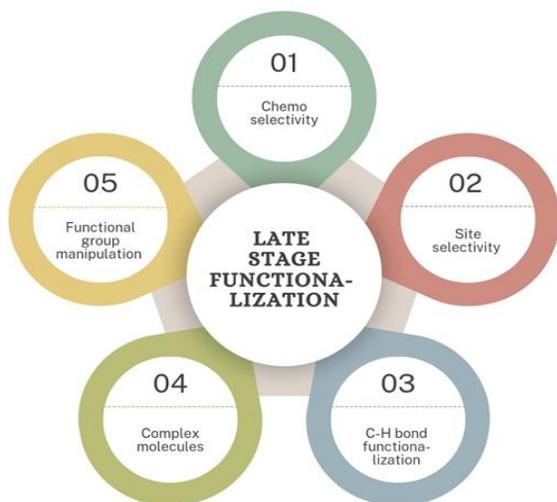


FIG NO. 5

The development of late-stage functionalisation (LSF) techniques, particularly C–H functionalisation, has revolutionised organic synthesis. Over the past ten years, medicinal chemists have been using LSF approaches into their systems to improve the efficiency of the drug development process. The main application of late-stage C–H functionalisation of pharmaceuticals and drug-like compounds has been to rapidly diversify screening libraries for the purpose of examining structure–activity relationships. Conversely, LSF techniques are being employed more frequently as a successful way to improve the drug-like molecular properties of potential therapeutic candidates.⁶⁷

V. GREEN AND SUSTAINABLE CHEMISTRY

Introduction:

By selecting no solvents or green solvents (ideally water), alternative reaction media, and taking into account one-pot synthesis, multicomponent reactions (MCRs), continuous processing, and process intensification techniques for atom economy and final waste reduction, the principles of green chemistry (GC) can be fully applied in the green synthesis of pharmaceuticals. A comprehensive design of the active pharmaceutical ingredient's (API) life cycle, reducing risks and pollution, and maximising the synthesis technique's resource efficiency can all be used to carry out GC in green synthesis.⁶⁸

The most important aspect of green chemistry is the concept of design. Design is a statement of human intention and cannot be created by accident. It includes creativity, planning, and systematic brainstorming. The 12 Principles of Green Chemistry are "design rules" that help chemists achieve the intentional goal of sustainability. Green chemistry is defined by careful planning of chemical synthesis and molecular design to reduce adverse effects. Appropriate design can lead to synergies rather than just trade-offs.⁶⁹

One of the key principles of green chemistry is the removal of solvents from chemical reactions or the replacement of hazardous solvents with environmentally acceptable ones. The ideal course of action is, of course, to create substitute procedures that don't need solvents. If a solvent is necessary for a process, substitute solvents that will have minimal to no impact on the environment and human health should be selected. Water, ionic and fluorinated liquids, supercritical media, and their many combinations are examples of alternative solvents that are being employed more and more.⁷⁰

Catalysis is a fundamental principle of green chemistry, which involves the development of chemical products and processes that reduce or eliminate the use and production of hazardous elements. The creation and application of innovative catalysts and catalytic systems are simultaneously achieving the goals of environmental protection and financial benefit. Green chemistry, which is the development of chemical products and processes that reduce or eliminate the use and manufacture of hazardous substances, is a comprehensive approach that may be applied to all aspects of chemistry.⁷¹

The material basis of a sustainable society will be provided by chemical products and processes that are made in accordance with principles that make them favourable to life. Important intrinsic properties of molecules must be considered from the outset the design stage in order to assess whether chemicals and processes are depleting versus renewable, dangerous versus benign, and persistent versus quickly degradable. Under a more comprehensive definition of performance that considers sustainability, the ideas of green chemistry must be integrated into products, feedstocks, and production processes. To accomplish this shift, the most cutting-edge scientific and inventive traditions must be blended with recently created systems thinking and systems design that

begins at the molecular level and has a positive impact on the global scale.⁷²

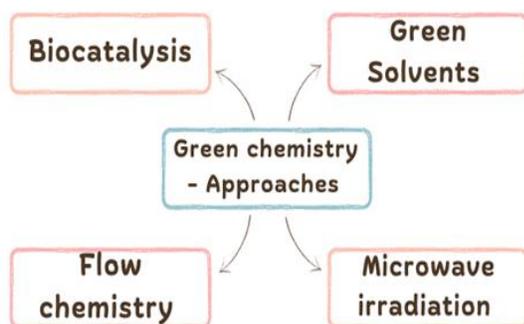


FIG NO. 6

VI. APPLICATION OF MICROWAVE IN SYNTHETIC CHEMISTRY



FIG NO. 7

Principles of green chemistry:

1. Preventing waste is preferable to treating or cleaning it up after it has already formed.
2. Synthetic techniques ought to be developed to optimize the integration of all process inputs into the finished product.
3. if possible, synthetic processes should be created to use and produce materials with low or no toxicity to the environment and human health
4. Chemical products ought to be made to minimize toxicity while maintaining function.

5. Wherever possible, auxiliary compounds (solvents, separation agents, etc.) should be avoided or used sparingly and in a harmless manner.
6. Energy needs should be minimized and acknowledged for their effects on the economy and environment.
7. Whenever it is technically and financially feasible, a feedstock or raw resource should be renewable rather than diminishing.
8. Whenever feasible, avoid unnecessary derivatization (blocking groups, protection and deprotection, and short-term changes to physical or chemical processes).
9. Catalytic agents outperform stoichiometric reagents in terms of selectivity.
10. Chemical goods ought to be made in such a way that, upon completion of their intended use, they decompose into harmless degradation products rather than remaining in the environment.
11. To enable real-time, in-process monitoring and control before the creation of hazardous chemicals, analytical methods must be further improved.
12. The selection of substances and their forms in a chemical process should minimize the risk of chemical accidents, such as releases, explosions, and fires.⁷³

Green Solvents:

The commercial manufacturing and service sectors make extensive use of solvents. Because they are hard to contain and recycle, they will always poison our air, land, and water, even with all the precautions taken. Therefore, researchers have concentrated on developing solvent-free technologies and more effective recycling procedures in order to reduce the usage of solvents. Nevertheless, these methods have drawbacks that call for a strategy to prevent contamination and the pursuit of environmentally friendly solvent substitutes.⁷⁴

Solvents are essential for most household and industrial applications. The impact of solvent losses and emissions drives efforts to minimise or completely eradicate them. In the 1990s, this became a major focus for green chemistry, giving rise to the idea of the "green" solvent. This concept has led to the development of so-called neoteric solvents and a sizable corpus of chemical literature.⁷⁵

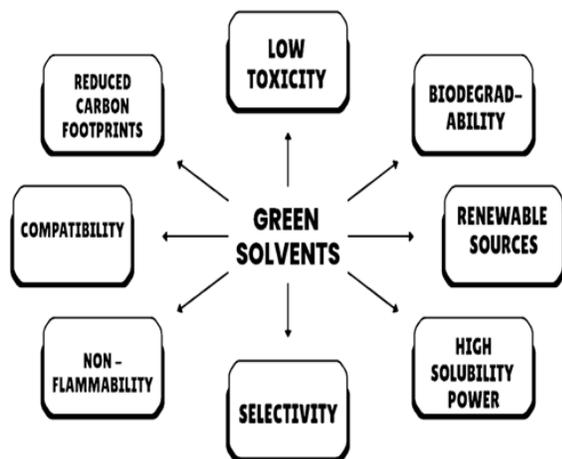


FIG NO. 8

Academic research in the subject of green solvents does not focus on the companies that use solvents the most or the kind of solvents that the study community believes have the best likelihood of minimizing solvent-related environmental harm.⁷⁶

Solvents define crucial properties for chemical processing and reactions, just like catalysts do. A solvent may be the key to a successful chemical process; it is more than just a tool and a space for reactions. It regulates the activation potential-energy curves by determining the solubility (i.e., the concentration at which reactants may be processed) and the stability of excited states. In general, solvents have a greater impact on productivity, the economy, and the environment. In an attempt to improve the capabilities of conventional solvents, a new class of so-called master solvents also known as "green" or "designer" solvents has been proposed and researched over the past 20 years. They include supercritical carbon dioxide and ionic liquids as well as deep eutectic, thermomorphic, and fluorosolvents.⁷⁷ In addition to defining a large part of the environmental performance of chemical industrial processes, solvents have an effect on health, safety, and cost. The idea of "green" solvents expresses the objective of lessening the environmental impact of solvent usage in chemical synthesis. This raises the question of how to determine the "greenness" of a solvent. We provide a comprehensive method for assessing the environmental impact of solvents that takes into account important aspects of solvents' environmental performance in chemical manufacturing as well as important health and safety issues. The approach

combines the assessment of substance-specific risks with the monitoring of emissions and resource consumption during a solvent's whole life cycle.⁷⁸

Laws and shifting public attitudes towards environmental issues have increased the significance of developing green solvents for extractions, separations, formulations, and reaction chemistry. There are currently a number of general-purpose solvent selection recommendations available with the goal of minimizing the use of the most dangerous solvents.⁷⁹

The increasing awareness of the pressing need for more sustainable and environmentally friendly technology has sparked interest in the use of atom-efficient catalytic processes for the synthesis of medicines and fine chemicals. Another area that is receiving increasing attention is the use of alternate reaction media, which circumvent the problems associated with many of the traditional volatile organic solvents. Using an unusual reaction media can also help with catalyst recovery and recycling.⁸⁰

The use of flammable and volatile organic solvents in various reaction systems and separation stages significantly affects a process's economic and environmental performance. Because of this, a growing area of research in the development of green technologies is concentrated on producing innovative, eco-friendly, and adaptable solvents whose use would meet both financial and technological requirements. Among the recommended solvents, room temperature ionic liquids, supercritical and subcritical fluids, and solvents generated from natural and renewable sources are the most promising approaches for current solvent innovation.⁸¹

VII. BENEFITS OF USING GREEN SOLVENTS IN SYNTHESIS

Green Solvents :

- Water
- Supercritical carbon dioxide
- Ionic liquids
- Polyethylene glycol and its solutions
- Fluorous solvents⁷³

1) Organic Synthesis in Water:

Scientists worldwide are conducting research in the aqueous phase due to the environmental

contamination that organic solvents produce. Using water as a solvent in processes has a number of possible benefits.

- 1) In comparison, water is a less expensive solvent. Chemical reactions can be made more cost-effective by using water as a solvent.
- 2) Water is a safe solvent that has none of the drawbacks of organic solvents, which include being flammable, possibly explosive, mutagenic, and/or carcinogenic.
- 3) Direct use is possible for compounds that dissolve in water. This will be especially helpful in the chemistry of fermentation, proteins, and carbohydrates.
- 4) Simple phase separation can be used to isolate the products in big industrial processes. Because water has one of the highest heat capacities of any substance, it is also simpler to regulate the reaction temperature.
- 5) One of the main concerns with utilizing volatile organic solvents is pollution, which may not be an issue when water is used as a solvent.
- 6) It is easy to recycle water.⁷³

Wurtz reaction:

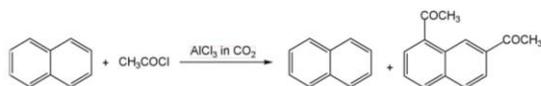
Coupling of alkyl halides with sodium in dry ether to give hydrocarbon⁸¹ is known as wurtz reaction.



2) Organic Synthesis in Supercritical Carbon Dioxide:

People did not know about CO₂ until the early sixteenth century. Farade first proposed the existence of several liquified gases, including CO₂, in 1823. In 1961, Gorel described how to make liquid CO₂. Nonetheless, the majority of research on the use of CO₂ as a solvent for natural product extraction began in 1960.

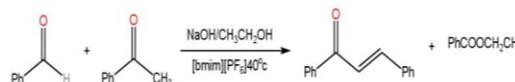
Freidel-Crafts Reaction:



3) Organic Synthesis using Ionic Liquids:

The goal of perfect synthesis is to create the target product with 100% yield and selectivity. Volatile organic compounds utilized in organic synthesis make up the majority of organic solvents used in industry. Many solvents, especially chlorinated hydrocarbons, have poisonous and dangerous qualities that make their use costly and cause major environmental problems such air emissions. Ionic liquids have recently emerged as a novel substitute for volatile organic chemicals, which have historically been employed as industrial solvents. They lessen the risks to human health, the environment, and volatility that come with exposure to organic solvents.

Claisen-Schmidt Condensation

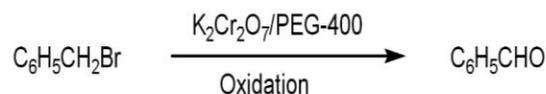


4) Organic Synthesis using Polyethylene Glycol and its Solutions:

The primary obstacle to the extensive use of water as a reaction solvent is the limited solubility of organic reactants and their intermediates. Polyethylene glycol (PEG) solutions have been discovered to be a superior substitute. Polyethylene glycol is thought to have the potential to become a green reaction medium in the future.

Oxidation Reaction:

Oxidation of benzyl bromide : K₂Cr₂O₇ is soluble in PEG-400 and can oxidise benzyl bromide to benzaldehyde in good yield.⁷³



VIII. CONCLUSION

Drug discovery, material design, and sustainable industrial practices are all fueled by synthetic chemistry, which continues to be the foundation of contemporary pharmaceutical innovation. Recent developments are broadening the chemical space and making more effective, selective, and ecologically

friendly processes possible. These developments range from AI-driven synthesis and flow chemistry to photo-redox catalysis, biocatalysis, and C–H activation. Green chemistry principles, on the other hand, emphasize how vital it is to incorporate sustainability into each step of synthesis in order to guarantee less waste, safer solvents, and increased resource efficiency. When combined, these developments not only speed up and improve the accuracy of chemical research, but they also point the way toward a more significant and sustainable future for synthetic chemistry.

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