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Current Trend in Organic Synthesis: A Review

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Abstract

The present organic synthesis trend encompasses the invention of novel methods for the efficient and selective synthesis of complicated chemicals, as well as the use of environmentally friendly and sustainable technologies. another aspect of emphasis is the use of computational methods to design and optimize synthetic pathways, as well as to predict the properties of new molecules. Additionally, there is a growing interest in the use of renewable starting materials and the creation of more sustainable synthetic processes. Overall, the field of organic synthesis is rapidly evolving to address the challenges of modern society, including the need for new materials, drugs, and technologies that are both effective and environmentally responsible.

Keywords: Organic Synthesis, Green Chemistry, Mechanochemistry, Combinatorial Chemistry

1. Introduction

The physicochemical transition that occurs when two or simpler molecules mix in a regulated manner to produce a more complex chemical product is referred to as chemical synthesis. Chemical synthesis is frequently significantly more complex than A+B = C and mixtures containing product and by-products can arise.

Chemical synthesis is used to create all commercially significant products in the pharmaceutical, polymer, fine, and bulk chemical industries. The efficient use of reactants and reagents via a thorough understanding and control of reaction variables is related to the success of a chemical synthesis, which is defined as creating the target molecule with the correct economics and quality.

All manufactured organic- and inorganic-based items generated to help civilization are the result of modern chemical synthesis. Modern chemical synthesis necessitates procedures that are well-understood, well-controlled, and generate products that fulfill economic, quality, and safety goals while minimizing environmental effect.

Organic chemistry is a constantly evolving discipline, and various current trends are impacting the future of research and development in this area. Some of the most significant trends in organic chemistry include:

1-Sustainable and Green Chemistry: The development of sustainable and green chemistry is a major trend in organic chemistry, focusing on the use of environmentally friendly and economically viable methods for the synthesis of organic compounds. This includes using renewable resources, reducing waste and pollution, and developing safer, more efficient chemical processes [1].

2-Medicinal Chemistry: Organic chemistry plays an important function in the growth of new pharmaceuticals and therapeutics. There is a growing trend towards the development of more effective drugs with fewer side effects, utilizing organic chemistry techniques such as combinatorial chemistry, high-throughput screening, and molecular modeling [2].

3- AI and Machine Learning: Machine learning and artificial intelligence are being used is becoming increasingly significant in organic chemistry, notably in drug design and materials science. These techniques are being used to accelerate the development of new compounds and materials, and to predict the properties of these materials based on their chemical structures [3].

1.1 Sustainable and Green Chemistry

Principles are increasingly being applied in the field of drug synthesis to minimize the environmental impact of the pharmaceutical industry and create a more secure and efficient system drug manufacturing processes. Here are some examples of how sustainable and green chemistry principles are being applied in drug synthesis:

1.1.1 Mechanochemistry

Mechanochemistry has a long and varied history, with the first accounts reaching back to the 4th century BC. Aristotle's disciple Theophrastus of Eresus is credited with the first documented mechanochemical reaction where he observed drops of liquid mercury made by using a copper mortar to grind up pieces of cinnabar. In modern times, mechanochemistry has evolved to become closely linked to supramolecular chemistry, with recent developments Mechanochemistry was utilized to synthesize complex organic compounds, supramolecular assemblies, and metal-organic frameworks. The simplest equipment used for mechanochemical reactions is the mortar and pestle, but automated grinding equipment like high-speed ball mills and mixer ball mills are widely used in laboratory and industrial processes [4, 5].

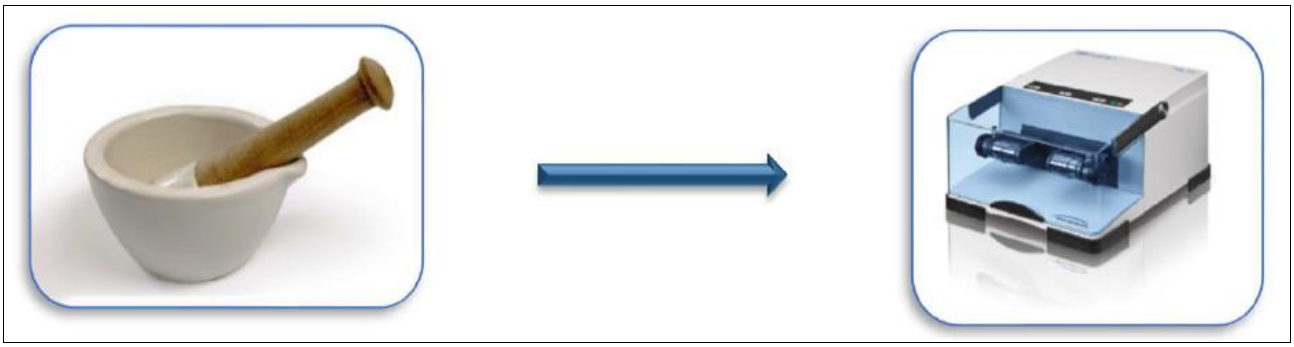


Fig 1: Mechanochemical reaction equipment [6]

The term "mechanochemistry" describes the application of mechanical power to chemical reactions. The mill reactor's Friction and banging of the spheres produces high-temperature microsites that encourage the substrate bonds to break and new bonds to form, producing the desired result [6].

Mechanochemistry offers several advantages over traditional solution-based methods, especially in terms of environmental and safety considerations. The absence of solvents or the utilization of very tiny amounts of it as a grinding assist, as well as the reduction in particle size, radical production, and energy consumption, is a considerable advantage. Mechanochemistry is also useful for reactions between insoluble materials, processes in which solvents can interfere, and reactions that are solvent sensitive. Furthermore, mechanochemistry allows for the elimination of toxic solvents, making processes safer and faster [5, 7, 8].

When compared to equivalent solution-based protocols, mechanochemical approaches can affect chemical reactivity and selectivity. As a result, solvent-free milling may produce various product formulations or equilibration mixes than solution milling. Milling reactions have also made it possible the capture and characterisation of Intermediates and materials that are difficult to come by [9].

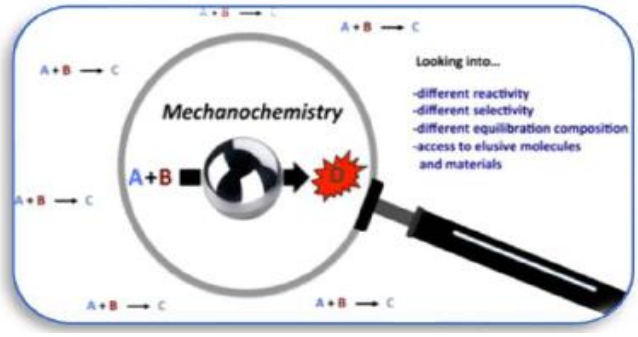
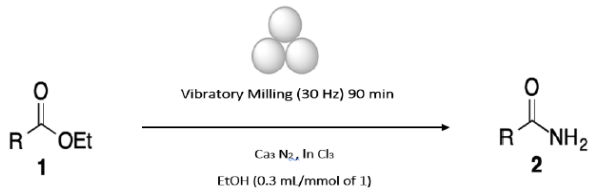


Fig 2: Altering Product Selectivity by Mechanochemistry

Application

Mechanochemistry has many potential applications, including the synthesis of primary amides from amines and carboxylic acids. This transformation is crucial in drug synthesis, and mechanochemical approaches have been developed to achieve it. Mall milling activation with calcium nitride is an appropriate way for this transformation that does not require chromatography and is suitable for various functional groups and stereocenters in close proximity to carbonyls as shown in scheme. Mechanochemistry has the potential to improve the efficiency and safety of chemical reactions, and its development is ongoing (10).

Fig 3: Primary Amide Synthesis



Scheme 1: Scope of the Mechanochemical Primary Amide Synthesis [10]

1.1.2 Microwave-Assisted Chemistry

Microwave-assisted synthesis is a technique that uses microwaves to accelerate chemical reactions. This technique reduces the amount of energy required for drug synthesis and can also reduce reaction times and improve yields [11].

Microwave-assisted chemistry, which has evolved into an indispensable tool in all fields of synthetic organic chemistry, including solvent-free and water-mediated processes. In the past, chemical synthesis was carried out using traditional methods like hot oil baths or burners, which were slow and inefficient. However, the invention of the microwave oven for heating food led to the use of microwave energy to accelerate chemical synthesis in the mid-1980s [12].

Fig 4: Modern Microwave reactor

Microwave irradiation produces distinct thermal effects that are extremely advantageous for chemical synthesis, and it is based on the efficient heating of materials via dielectric heating effects. This method of heating produces homogeneous and selective heating, faster reactions, less byproducts, higher yields, and easier set-up. Microwave-assisted chemical reactions are already well-established laboratory methods.

Despite the fact that there are advantages, microwave technology has some disadvantages, such as high investment costs, unsuitability for scale-up, and limited applicability for materials that absorb them. The text concludes that microwave-assisted chemistry has several applications, including green synthesis, and highlights its potential to accelerate chemical synthesis and expand the creativity of chemists [13, 14].

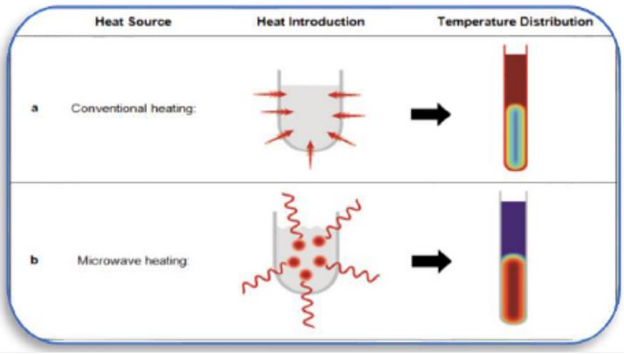
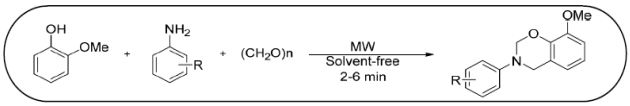


Fig 5: Graphical illustration of heat introduction and temperature distribution in (to) a reaction mixture for (a) conventional heating and (b) microwave heating

Application

Microwave-Assisted Solvent-Free Synthesis of Novel Benzoxazines:

In 2017, Lomonaco *et al.* reported the synthesis of benzoxazines in the absence of solvent using an environmentally friendly microwave-assisted technique. Benzoxazines are useful intermediates in the production of resins used in the polymer and synthetic materials industries. As indicated in Scheme 2, this study offers the synthesis of a family of compounds produced with quick reaction durations of 2-6 minutes and moderate to good yields [5, 15].



Scheme 2: Microwave synthesis of benzoxazines under solvent-free conditions

1.1.3 Photocatalysis Synthesis

Photocatalysis synthesis is a chemical reaction that happens when photocatalyst is used to facilitate a chemical reaction through exposure to light. The history of photocatalysis synthesis can be traced back to more than 100 years ago when Giacomo Ciamician suggested the replacement of processes generally used for chemical transformations with reactions that green plants apply, which are essentially based on photochemical reactions induced by solar light and enzymatically catalyzed reactions [16].

The use of photocatalysts can provide numerous benefits such as chemical-physical stability, low cost, and environment friendliness, and it can be a clean and renewable energy source. Photocatalysis synthesis has many potential applications in fields such as pharmaceuticals, environmental remediation, and energy production [17].

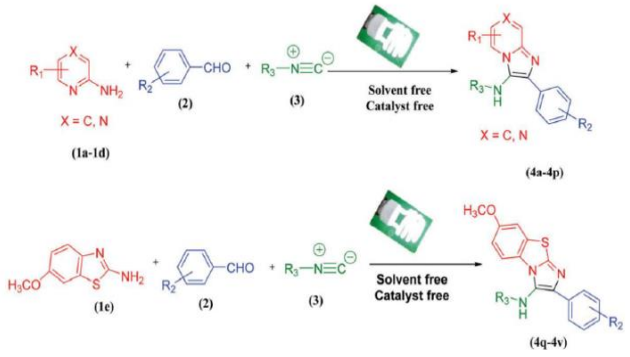
Fig 6: Advantages of photocatalysis

However, the efficiency of photocatalysis is limited, especially for nonvisible-light driven ability, and the low usage of visible light limits the industrial applications of the present photocatalytic system. Despite the disadvantages, photocatalysis synthesis is a powerful tool that has the capability to facilitate a diverse set of chemical reactions

and to enable the synthesis of new materials and compounds with useful properties [18].

An example of the application of photocatalysis synthesis is the synthesis of imidazo [1, 2-a] pyridines and imidazo [2, 1-b] thiazoles under catalyst and solvent-free conditions, which are crucial in medicinal chemistry because of their broad range of pharmacological and biological activities.

In 2018, Siddiqui and colleagues disclosed a photocatalyzed technique for the synthesis of imidazole pyridines and imidazole thiazoles without the use of a catalyst and using only visible light as an activator [5, 19].



Scheme 3: Model reactions for the synthesis of imidazo[1, 2-a] pyridine and imidazo[2,1-b] thiazole derivatives

The importance of sustainable and green chemistry in drug synthesis is becoming increasingly recognized by regulatory agencies. For example, the United States Food and Drug Administration (FDA) has developed guidelines for the use of green chemistry principles in pharmaceutical manufacturing. These guidelines encourage the use of more sustainable and environmentally friendly processes in drug synthesis.

In addition to the environmental benefits, the application of sustainable and green chemistry principles in drug synthesis can also lead to the development of safer and more efficient drug manufacturing processes. This can ultimately result in lower costs and better access to life-saving medications for patients.

1.2 Medicinal Chemistry

Organic chemistry plays a crucial function in the development of new pharmaceuticals and therapeutics. There is a growing trend towards the development of more effective drugs with fewer side effects, utilizing organic chemistry techniques such as combinatorial chemistry, high-throughput screening, and molecular modeling.

Medicinal chemistry is an interdisciplinary field centered on the discovery and advancement of new drugs. It involves the synthesis and design of compounds with the goal of identifying novel therapeutics that can be used to treat a variety of diseases. The importance of medicinal chemistry in drug synthesis lies in its ability to create compounds with improved pharmacokinetic and pharmacodynamic properties, as well as enhanced selectivity and reduced toxicity [2].

1.2.1 Combinatorial Chemistry

Combinatorial chemistry is a powerful technique used in drug discovery and development that allows for the synthesis and screening of large numbers of chemical compounds in a brief amount a short amount of time. This approach involves the synthesis of libraries of diverse molecules that are tested for biological activity against a specific target or disease.

Combinatorial chemistry can be used to generate a great number of compounds with varying structures and properties, which can then be screened for prospective medication candidates. This approach can greatly increase the efficiency of drug discovery while shortening the time and cost associated with traditional drug development [20].

One common method used in combinatorial chemistry is solid-phase synthesis, which involves the use of a solid support, such as resin beads, to facilitate the synthesis of large numbers of compounds. This approach allows for rapid synthesis and purification of compounds, and can be easily automated to further increase efficiency.

Another method used in combinatorial chemistry is parallel synthesis, which involves the simultaneous synthesis of multiple compounds in separate reaction vessels. This approach can be used to rapidly generate large numbers of compounds with varying properties and structures [21].

Combinatorial chemistry has been employed to develop a large variety of drugs, such as antibiotics anticancer agents, and drugs for treating cardiovascular and metabolic diseases. By enabling the rapid synthesis and screening of large numbers of compounds, combinatorial chemistry has greatly accelerated the pace of drug discovery and has the capability to lead to the creation of new and more effective therapeutics [22].

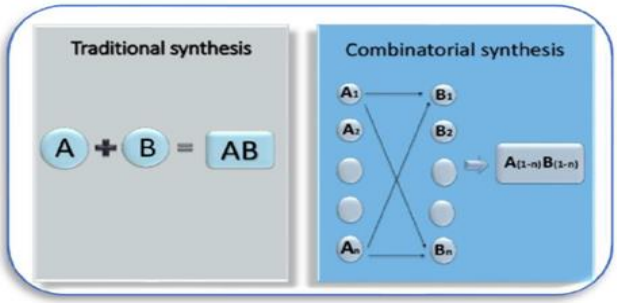


Fig 7: Comparison between traditional synthesis and combinatorial synthesis

1.2.2 High Throughput Screening

High-throughput screening (HTS) is a technique used in drug discovery to evaluate a large number of compounds quickly for potential biological activity against a specific target. This approach involves the use of automated platforms to evaluate hundreds of thousands of chemicals in a single trial.

One common method used in HTS is fluorescence-based assays, which involve the use of fluorescent tags to detect changes in protein function or binding. Another method used in HTS is label-free assays, which rely on changes in the physical or chemical properties of molecules to detect binding or activity [23].

HTS has greatly increased the efficiency and speed of drug discovery, allowing for the screening of large numbers of compounds in a brief amount of time. This approach has led to the discovery of several important drugs, including HIV protease inhibitors, anticancer agents, and drugs for treating cardiovascular and metabolic diseases [24].

While HTS has many advantages, it also has some limitations, including the high cost of instrumentation and reagents, as well as the potential for false positives or false

negatives. As such, it is important to carefully validate and confirm any hits from HTS before moving forward with drug development [25].

1.2.3 Molecular Modeling

Molecular modeling is a powerful computational tool used in drug discovery to predict the interactions between small molecules and target proteins, as well as to optimize the chemical properties of drug candidates. There are several types of molecular modeling techniques, including docking, and quantitative structure-activity relationship (QSAR) analysis are all examples of molecular dynamics simulations.

Molecular dynamics simulations involve the simulation of the movement of atoms and molecules over time to study the behavior of proteins and their interactions with ligands. [26]

Docking is a computer technique for predicting a ligand's binding orientation and affinity to a protein target. QSAR analysis is a quantitative examination of the link between a compound's chemical structure and its biological activity. Deep Docking use QSAR models trained on actual docking scores from a small subset of a molecular database to predict docking scores for the remainder.

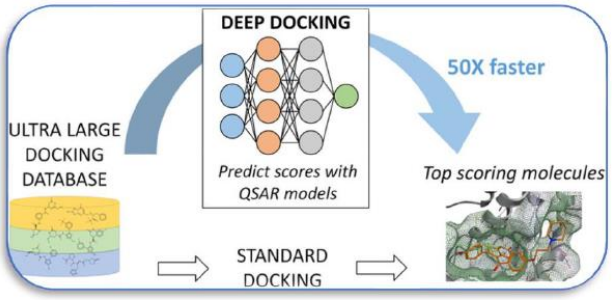


Fig 8: Deep Docking

Molecular modeling has become an essential tool in drug discovery, allowing for the rapid a vast number of chemicals are screened and the identification of possible pharmaceutical candidates with high binding affinity and selectivity for their target proteins. This approach has led to the discovery of several important drugs, including HIV protease inhibitors and anticancer agents [27, 28].

One major advantage of molecular modeling is that it allows for the optimization of drug candidates before experimental testing, lowering the time and expense of medication development. Additionally, molecular modeling can provide insights into the mechanism of drug action, aiding in the design of more effective and targeted drugs [29].

One application illustration of medicinal chemistry in drug synthesis is the development of the anti-cancer drug Imatinib. Imatinib was designed to selectively inhibit the activity of a specific protein, tyrosine kinase, which is overactive in certain types of cancer. Medicinal chemists used structure-based drug design to develop a compound that could bind selectively to the active site of tyrosine kinase, resulting in a highly effective anti-cancer drug [30].

Another example is the development of the HIV drug Darunavir. Darunavir was developed using a combination of medicinal chemistry and computational modeling techniques. Medicinal chemists designed the drug to target the active site of the HIV protease enzyme, while computational modeling was used to optimize the structure of the drug to improve its binding affinity and selectivity [31].

In addition to the development of new drugs, medicinal chemistry plays an important function in the optimization of existing drugs. By modifying the chemical structure of existing drugs, medicinal chemists can improve their pharmacological properties, such as increasing their potency or reducing their toxicity. This process is known as drug optimization, and it is an important component of drug development [32].

One example of drug optimization is the development of the anti-coagulant drug Apixaban. Apixaban was designed as an improvement over existing anti-coagulant drugs, such as Warfarin, which have a narrow therapeutic window and require frequent monitoring. Medicinal chemists used structure-based drug design to develop a compound that could selectively inhibit a specific blood-clotting protein, resulting in a drug with improved efficacy and safety [33].

Overall, medicinal chemistry is a vital field that is essential in drug discovery and development. By applying a range of techniques and approaches, medicinal chemists are able to identify and optimize compounds with therapeutic potential, leading to the development of novel medications to treat a range of disorders. As our understanding of disease biology and drug targets continues to evolve, the significance of medicinal chemistry in the creation of pharmaceuticals is only likely to grow [34].

1. 3 Machine Learning and Artificial Intelligence

Machine learning and artificial intelligence are also becoming more essential in organic chemistry, particularly in drug design and materials research. These techniques are being used to speed up the synthesis of new chemicals and materials, as well as to anticipate their qualities based on their chemical structures [3].

Machine learning (ML) and artificial intelligence (AI) have transformed several industries, including medication discovery and development. In recent years, there has been an increasing interest in employing ML and AI to accelerate drug discovery, cut costs, and enhance success rates.

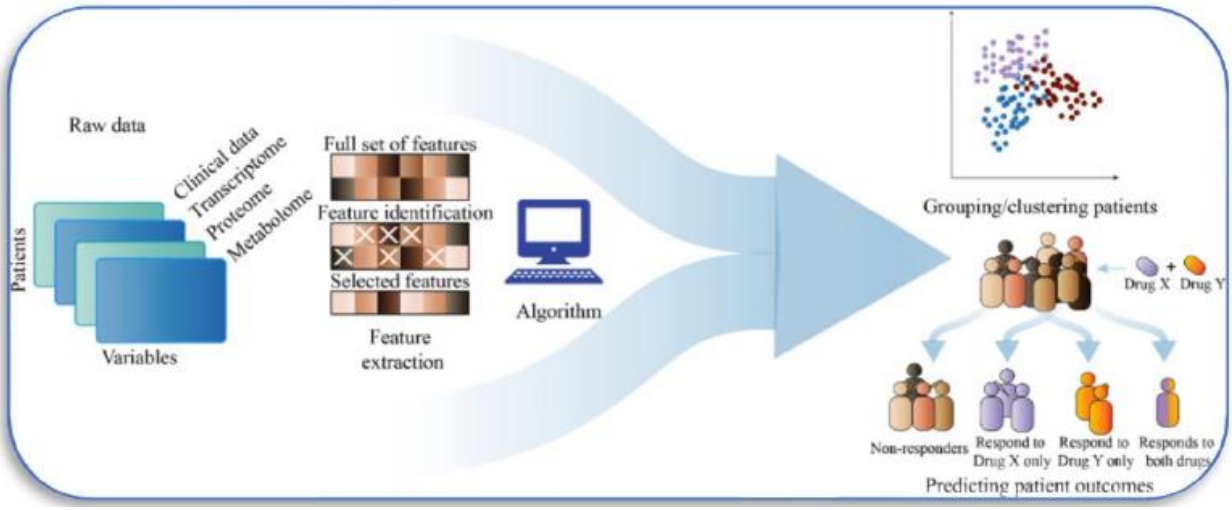


Fig 9: Process of AI/ML in translational medicine

One important ML and AI in drug manufacturing is in the prediction of the biological activity of compounds. By examining massive datasets of chemical and biological data, ML algorithms are capable of detecting patterns and relationships between the structure of a molecule and its biological activity. This can help medicinal chemists to design new compounds with improved activity profiles, or to optimize the properties of existing compounds [35].

Another application of machine learning and artificial intelligence in drug synthesis is in the prediction of the pharmacokinetic properties of compounds. By analyzing data on the absorption, distribution, metabolism, and excretion (ADME) of compounds, ML algorithms can predict how a compound will behave in the body, and help to identify potential safety concerns. This can help medicinal chemists to optimize the properties of compounds to improve their safety and efficacy [36].

ML and AI are also being used to design and optimize chemical reactions. Through the examination of big databases of chemical interactions, Machine learning algorithms can recognize patterns and relationships between the structure of a molecule and the conditions required for a reaction to occur. This can help chemists to design more efficient and selective reactions, reducing the time and cost required for synthesis [37].

AI and machine learning can potentially be utilized to speed up the drug repurposing process. The process of finding new therapeutic uses for existing medications is known as drug repurposing. Researchers can use ML and AI to examine vast databases of chemical and biological data to uncover potential new uses for approved medications or pharmaceuticals that failed in clinical trials. Because the safety and toxicity of the repurposed medications have already been verified, this technique can reduce the time and expense required for therapeutic development.

ML and AI can also be used to predict the safety of compounds, particularly their potential for toxicity. By analyzing large datasets of toxicity data, ML algorithms can predict the toxicity of new compounds before they are tested in animals or humans. This can help to reduce the need for animal testing, as well as reducing the risk of toxicity in clinical trials [38].

Overall, ML and AI have the potential to revolutionize drug synthesis, enabling faster and more efficient discovery of new drugs. However, the application of these techniques requires careful consideration of the quality and diversity of the data used, as well as the need to balance speed and efficiency with safety and efficacy considerations [39].

One of the key challenges in the application of ML and AI in drug synthesis is the requirement for high-quality, varied data. ML and AI algorithms rely on a huge number of chemical datasets and biological information to recognize patterns and linkages but these datasets can be biased or incomplete, which can lead to inaccurate predictions and suboptimal drug design [40].

To address this challenge, there is a growing emphasis on data sharing and collaboration in the drug discovery community. Initiatives such as the Collaborative Drug Discovery (CDD) platform and the Open PHACTS project aim to provide open access to large, high-quality datasets of chemical and biological information, which can be used to train ML and AI algorithms and facilitate drug discovery and development [41].

Overall, the use of machine learning and artificial intelligence in drug synthesis is an intriguing and fast expanding topic that has the potential to alter the drug discovery and development process. Researchers can accelerate drug development, cut costs, and improve the safety and efficacy of novel medications by using massive datasets of chemical and biological information [42].

Personalized medicine is one potential application of ML and AI in medication production. Personalizing therapies for individual patients based on genetic, environmental, and lifestyle factors is what personalized medicine is all about. ML and AI algorithms can be used to analyze large datasets of patient information, such as genomics and clinical records, to identify patterns and relationships that can be used to develop personalized treatments [43, 44].

2. Conclusion

The present direction in organic synthesis centers on creating fresh and effective techniques to synthesize intricate molecules, emphasizing sustainability and eco-friendliness. Moreover, computational methods are employed to optimize synthetic pathways and forecast the properties of new molecules. The significance of using renewable raw materials and sustainable synthetic processes is increasing, aligned with the need to tackle current challenges. Organic synthesis is evolving at a swift pace to cater to society's demand for novel materials, drugs, and

technologies that are effective and environmentally responsible. The current trend signifies a shift toward more sustainable and responsible chemical practices, providing opportunities for developing novel molecules to address significant societal requirements.

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