SCIREA Journal of Chemistry
ISSN: 2995-6943
http://www.scirea.org/journal/Chemistry
January 9, 2024
Volume 9, Issue 1, February 2024
https://doi.org/10.54647/chemistry150337

Development Trends in Chiral Drug Synthesis Techniques

Zhao Mingrui[1, *], Xu Zhanhui[2], Yang Ninghui[1]

[1] College of Pharmacy, Henan Medical College, Zhengzhou, China,451191

[2] College of Chemistry, Zhengzhou University，Zhengzhou, China,450052

Email address: zhaomingrui99@163.com

*Corresponding author

Abstract

The research and application of chiral drugs has attracted increasing attention, to explore the development trends of chiral drug synthesis technology,this paper introduce related green chemistry and emerging technologies, elaborates on the application of green chemistry in chiral drug synthesis, including catalyst design and utilization, solvent selection, and waste management. These green chemistry methods can significantly reduce environmental pollution and resource consumption, improve synthesis efficiency, and make chiral drug synthesis more sustainable and efficient. At the same time, this paper also introduces the application of some emerging technologies and equipment in chiral drug synthesis. These emerging technologies include microfluidic technology, electrochemical synthesis, solid-phase synthesis, and so on. The application of these technologies and equipment can effectively improve the synthesis efficiency and yield of chiral drugs, and have stronger controllability and selectivity. In addition, important experimental devices and instruments such as stereoisomers and nanoscale catalysts are also introduced, which provide effective tools and methods for chiral drug synthesis research. In summary, this paper systematically

studies and summarizes the development trends of chiral drug synthesis technology. Through the application of green chemistry and emerging technologies, providing important guidance and reference for the research and application of chiral drugs. This research has important scientific significance and application value in promoting the development and innovation of chiral drugs.

Keywords: Chiral Drug Synthesis Techniques, Development Trends, Chiral Drug

1 Introduction

Chiral drugs play a vital role in modern medicine. Many pharmaceuticals consist of chiral compounds, and the chirality of drugs can significantly influence their biological activities, pharmacokinetics, and toxicity. For example, the notorious drug thalidomide demonstrated how the enantiomers of a chiral drug can have drastically different effects - one enantiomer resulted in severe birth defects, while the other showed sedative properties. Thus, the development of efficient and selective methods for the synthesis of chiral drugs is of great importance. In recent years, the research and application of chiral drugs have attracted increasing attention. Chiral drugs, which possess asymmetric carbon centers, often exhibit different pharmacological activities and bioavailabilities compared to their racemic counterparts. Therefore, the synthesis and separation of chiral drugs are crucial in the pharmaceutical industry. [1-5]

Traditionally, the synthesis of chiral drugs has mainly relied on processes such as resolution, asymmetric synthesis, and enzymatic reactions. Resolution involves the separation of enantiomers, usually by utilizing their differences in physical properties or through the use of chiral resolution agents. However, this method often suffers from low yield and limited scalability. Asymmetric synthesis, on the other hand, involves the introduction of chirality using chiral catalysts or reagents. While this approach allows for the efficient synthesis of enantiomerically pure compounds, the development of new chiral catalysts and optimization of reaction conditions are still ongoing challenges.

Here, we will explore the development trends in chiral drug synthesis, with a specific focus on the integration of green chemistry principles and emerging technologies. We will discuss the applications of green chemistry in various aspects of chiral drug synthesis, including catalyst

design and utilization, solvent selection, and waste management. Additionally, we will introduce some emerging technologies and equipment, such as stereoisomeric oscillators and nanoscale catalysts, that have provided valuable tools and methodologies for chiral drug synthesis.

2 Green Chemistry in Chiral Drug Synthesis

2.1 Principles of Green Chemistry

Green chemistry, also known as sustainable chemistry, is a research field that focuses on developing chemical processes and products that are environmentally friendly, economically viable, and socially responsible. It aims to minimize the use and generation of hazardous substances, reduce energy consumption, and promote the efficient use of resources. In the context of chiral drug synthesis, green chemistry provides a sustainable approach to meet the increasing demand for chiral drugs while minimizing the environmental impact.

There are several principles that define green chemistry. One of the key principles is the use of renewable feedstocks and raw materials. By utilizing renewable resources, such as plant-based starting materials or bio-based catalysts, the reliance on non-renewable fossil fuels can be reduced. This not only reduces environmental pollution but also ensures long-term availability of resources.

Another principle of green chemistry is the design of safer chemicals. This involves minimizing the use of hazardous substances and replacing them with less toxic alternatives. In chiral drug synthesis, this principle can be applied by using greener solvents that are less harmful to human health and the environment. For example, water is often considered a green solvent due to its low toxicity and abundance.

Furthermore, green chemistry emphasizes the importance of energy efficiency. Energy-intensive processes in chiral drug synthesis can be optimized by using catalysis, which allows reactions to proceed at lower temperatures and pressures. Transition metal catalysts, such as palladium or ruthenium complexes, have been widely used in chiral drug synthesis to achieve higher reaction rates and selectivities.

In addition to these principles, green chemistry also promotes the prevention of waste generation. This can be achieved through the use of atom-efficient reactions, where the majority of the reactants are converted into the desired product without generating waste.

Moreover, the recycling and reuse of catalysts and solvents can further reduce waste and increase the overall efficiency of the synthesis.

2.2 Applications of Green Chemistry in Chiral Drug Synthesis

The principles of green chemistry have been successfully applied in the synthesis of chiral drugs, leading to more sustainable and environmentally friendly processes. This section discusses the applications of green chemistry in chiral drug synthesis, focusing on catalyst design and usage, solvent selection, and waste management.

2.2.1 Catalyst Design and Usage

Catalysis plays a crucial role in chiral drug synthesis, as it enables the selective formation of chiral products [6,7]. Green chemistry approaches in catalyst design aim to improve the efficiency and selectivity of catalytic reactions while minimizing waste. For example, the development of homogeneous catalysts with high turnover frequencies and selectivity has facilitated the synthesis of chiral intermediates and active pharmaceutical ingredients (APIs). Additionally, immobilized catalysts, such as supported metals or enzymes, offer advantages in terms of catalyst recovery, reuse, and reduced metal leaching.

2.2.2 Solvent Selection

The choice of solvents in chiral drug synthesis is a critical factor in achieving green and sustainable processes. Traditional solvents, such as dichloromethane or chloroform, are not environmentally friendly due to their high toxicity and potential for ozone layer depletion. Green solvents, on the other hand, are characterized by low volatility, low toxicity, and biodegradability. For example, ionic liquids, supercritical fluids, and water-based solvents have emerged as promising alternatives in chiral drug synthesis, offering improved reaction rates, selectivity, and recyclability.

2.2.3 Waste Management

Efficient waste management is an integral part of green chemistry principles. In chiral drug synthesis, waste can be minimized through the development of efficient reaction conditions, such as one-pot and multi-component reactions, which reduce the number of reaction steps and by-products. For example, magnetic ketoibuprofen molecularly imprinted nanomaterials were rapidly synthesized by using computer molecular simulation and one-pot method, high sensitivity detection of NSAIDs in complex samples by High-performance liquid chromatography has provided a new idea for the rapid preparation of magnetic molecularly

imprinted materials and environmental detection. [8]

Moreover, the integration of continuous flow technologies allows for real-time monitoring and control of reactions, leading to improved product quality and reduced waste generation.

Additionally, the use of recyclable or biodegradable materials, such as resins or polymers, as reaction media or support matrices can facilitate the separation and recovery of products and catalysts.

2.3 Advantages and Challenges of Green Chemistry in Chiral Drug Synthesis

Green chemistry offers numerous advantages in the synthesis of chiral drugs, making it a highly desirable approach for pharmaceutical industry. Some of the key advantages include improved process efficiency, reduced environmental impact, and enhanced sustainability.

One of the main advantages of green chemistry in chiral drug synthesis is the improved process efficiency. By using greener solvents, catalysts, and reaction conditions, the overall reaction yield and selectivity can be increased. This leads to higher productivity and reduced production costs, which are crucial factors in pharmaceutical industry. For example, Ibuprofen, non-steroidal anti-inflammatory drug, was synthesized using Brown-method of Boots' company, which requires a six-step process to produce ibuprofen from isobutyl-benzene. Only a portion of the raw material in each step enters the product, it's about 40% of the atoms in the raw material enter the final product. The synthetic route is as follows.

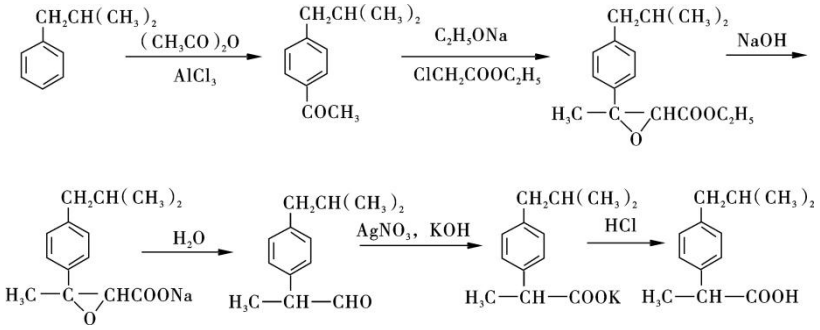

Figure 1 six-step process to produce ibuprofen

The BHC company invented a new method of producing ibuprofen. The product, ibuprofen, can be obtained by the new method using only three steps. Ibuprofen is produced by a new method, and its atomic economy reaches 77%, More than 99% if the recovery of by-product acetic acid is taken into account, that is to say, the waste generated by the new method is reduced by 37%.

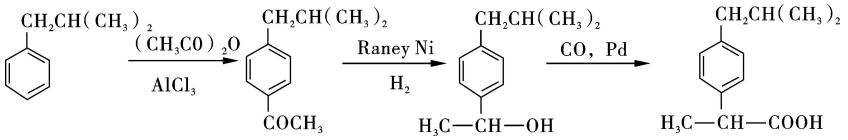

Figure 2 three-step method of producing ibuprofen

Furthermore, green chemistry techniques can significantly reduce the environmental impact of chiral drug synthesis. By minimizing the use and generation of hazardous substances, the release of toxic chemicals into the environment can be mitigated. This not only ensures the safety of the workers and surrounding communities but also contributes to the overall sustainability of the pharmaceutical industry.

Despite its numerous advantages, green chemistry in chiral drug synthesis also faces several challenges. One of the main challenges is the limited availability of green solvents and catalysts. While there has been significant progress in the development of greener alternatives, their commercial availability and scalability can still be a limiting factor. Additionally, the integration of green chemistry principles into established pharmaceutical processes often requires significant changes in infrastructure and mindset, which can be time-consuming and challenging.

In conclusion, green chemistry has emerged as a promising approach for the synthesis of chiral drugs. By applying the principles of green chemistry, such as the use of renewable raw materials, safer chemicals, energy efficiency, and waste prevention, the synthesis of chiral drugs can become more sustainable, efficient, and environmentally friendly. However, further research and development are required to overcome the challenges and fully realize the potential of green chemistry in chiral drug synthesis.

3 Emerging Technologies and Equipment in Chiral Drug Synthesis

3.1 Artificial Intelligence in Chiral Drug Synthesis

Artificial intelligence (AI) has emerged as a powerful tool in various scientific and technological domains, and its application in chiral drug synthesis is no exception. AI techniques, such as machine learning and deep learning algorithms, have been increasingly employed to predict reaction outcomes, optimize reaction conditions, and design new chiral catalysts.

One of the key advantages of AI in chiral drug synthesis is its ability to analyze and model

large datasets, which can help researchers explore the vast chemical space more efficiently. By training AI models on existing experimental data, researchers can predict reaction yields, selectivity, and enantio-selectivity, saving time and resources that would otherwise be spent on extensive experimental trials.

AI algorithms can also assist in the design of new chiral catalysts, by analyzing the structure-activity relationships of known catalysts and generating novel catalysts with improved performance. This approach has the potential to accelerate the discovery of highly efficient and selective chiral catalysts, which are crucial for the synthesis of enantiomerically pure drugs.

Furthermore, AI can optimize reaction conditions by taking into account multiple reaction parameters, such as temperature, pressure, and solvent choice. By analyzing the interactions between these parameters and reaction outcomes, AI algorithms can identify optimal reaction conditions that maximize the desired chiral product yield and enantiomeric excess.

In summary, the application of AI in chiral drug synthesis holds great promise for accelerating the development of new drugs and improving the efficiency of their synthesis. By leveraging the power of AI algorithms, researchers can overcome the challenges associated with the complexity and variability of chiral reactions, ultimately leading to the production of safer and more effective chiral drugs.

3.2 New Technologies in Chiral Drug Synthesis

In addition to AI, several other emerging technologies have also been adopted in the field of chiral drug synthesis, enabling more efficient and selective synthesis of chiral drugs. Two of these technologies are microfluidics and electrochemical synthesis.

Microfluidics involves the manipulation of small amounts of fluids in microscale channels, allowing for precise control of reaction conditions and reagent concentrations. [9-11] This technology offers several advantages over traditional batch reactions, including enhanced mass transfer, reduced reaction times, and improved reaction selectivity. In chiral drug synthesis, microfluidics has been successfully utilized for the rapid screening of reaction conditions, the optimization of reaction parameters, and the synthesis of complex chiral molecules.

Electrochemical synthesis, on the other hand, utilizes electrical energy to drive chemical reactions. This approach offers several benefits, such as milder reaction conditions, higher selectivity, and compatibility with a wide range of substrates. Electrochemical methods have

been successfully applied to the synthesis of chiral drugs, including the enantioselective functionalization of organic molecules and the synthesis of chiral building blocks. Moreover, electrochemistry can enable the use of renewable energy sources, making chiral drug synthesis more sustainable and environmentally friendly. [12-15]

3.3 Innovative Equipment in Chiral Drug Synthesis

Apart from new technologies, innovative equipment has also played a crucial role in advancing chiral drug synthesis. One important piece of equipment is the stereoscope, which allows chemists to visualize and analyze the three-dimensional structures of molecules. By obtaining a better understanding of the spatial arrangement of atoms in chiral molecules, researchers can design more effective synthetic routes and develop new chiral catalysts. [16]

Another significant innovation in chiral drug synthesis is the development of nanoscale catalysts. [17,18] These catalysts, which typically consist of metal nanoparticles, exhibit exceptional catalytic activity and selectivity due to their high surface area and unique electronic properties. Nano-catalysts have been employed in various chiral transformations, including hydrogenation, oxidation, and asymmetric synthesis. Their small size and efficient catalytic performance make them ideal candidates for the synthesis of chiral drugs with high enantio-selectivity.

Other innovative equipment includes advanced analytical techniques, such as high-performance liquid chromatography (HPLC) and nuclear magnetic resonance (NMR) spectroscopy. [19,20] HPLC allows for the separation and analysis of chiral compounds, while NMR spectroscopy provides valuable information about the stereochemistry and purity of chiral drugs. These techniques enable researchers to characterize and quantify chiral compounds with high precision, ensuring the quality and consistency of chiral drug synthesis.

In conclusion, the development of new technologies and innovative equipment has revolutionized chiral drug synthesis, making it more efficient, selective, and sustainable. The application of AI, microfluidics, electrochemical synthesis, and innovative equipment has enabled researchers to overcome the challenges associated with chiral reactions and accelerate the discovery of new chiral drugs. By leveraging these emerging technologies and utilizing advanced equipment, the synthesis of chiral drugs can be further optimized, ultimately leading to the development of safer and more effective pharmaceuticals.

4 Conclusion

With the increasing demand for chiral drugs and the need for sustainable and environmentally friendly synthesis methods, researchers have been exploring the integration of green chemistry principles into chiral drug synthesis. Green chemistry aims to reduce the environmental impact of chemical processes by optimizing the use of resources, minimizing waste generation, and maximizing energy efficiency. By incorporating green chemistry principles, the synthesis of chiral drugs can be made more efficient, environmentally friendly, and economically viable.

Furthermore, emerging technologies and equipment have also contributed to advancements in chiral drug synthesis. Microfluidic technology, for instance, allows for precise control over reaction conditions and rapid screening of reaction parameters, leading to improved reaction efficiency and selectivity. Electrochemical synthesis offers an alternative approach to traditional chemical synthesis, enabling the direct functionalization of complex molecules under mild conditions. Solid-phase synthesis, commonly used in peptide synthesis, has also found applications in the synthesis of chiral drugs, allowing for rapid synthesis and purification.

Overall, this paper provides a comprehensive study and summary of the development trends in chiral drug synthesis techniques. Through the application of green chemistry principles and emerging technologies, the synthesis of chiral drugs can be made more efficient, environmentally friendly, and sustainable. This research has significant scientific and practical implications in promoting the development and innovation of chiral drugs, ultimately improving their quality, efficacy, and accessibility.

Acknowledgements

This work was supported by Science and Technology Department of Henan Province under Grant NO. [2020] 22.

References

[1] Emerging Developments in Separation Techniques and Analysis of Chiral Pharmaceuticals.Molecules,2023,28

[2] P. Ferreira, D. Arcanjo, A. Peron. Drug development, Brazilian biodiversity and political choices: Where are we heading? Journal of Toxicology and Environmental Health. Part B, Critical Reviews,2023,26:257 - 274

[3] Skipped Fluorination Motifs: Synthesis of Building Blocks and Comparison of Lipophilicity Trends with Vicinal and Isolated Fluorination Motifs. Journal of Organic Chemistry,2021

[4] Chiral stationary phases and applications in gas chromatography. Chirality,2022

[5] Zhou Qilin, Asymmetric catalytic kinetic resolution and its application[J]. Tianjin, Nankai University ,2020-12-29.

[6] T. Sudha. Chemistry and euro green chemistry recent trends in the separation of chiral drugs.2019

[7] Zhou Qilin, Highly efficient asymmetric catalytic reactions and their applications in the synthesis of natural products and chiral drugs[J], Tianjin,Nankai University,2015-04-24.

[8] Youfang Huang, Yanyun Li, Yuanfei Wu, etal. Computer-aided design-based green fabrication of magnetic molecularly imprinted nanoparticles for specific extraction of non-steroidal anti-inflammatory drugs[J]. Chemical Engineering Journal 452(2023)139440

[9] Fu Qiang. Research and implementation of a microfluidic device for rapid detection of nucleic acids[D]. Beijing university of chemical technology,2023. DOI:10.26939/d.cnki.gbhgu.2023.000321.

[10] Du Peng, Zhou Qingzhong, Zheng Hanwen,etal. Research progress of microchannel cooling technology for high-density integrated microsystems[J]. Microelectronics & Computer,2023(01):87-96 https://doi.org/10.19304/J.ISSN1000-7180.2022.0810.

[11] Yang Yuchi, Lv Peiyu,Du Jianyu,etal. Embedded microfluidic cooling technology for large area processing chip[J]. Microelectronics & Computer,2023(01):105-123 https://doi.org/10.19304/J.ISSN1000-7180.2022.0765.

[12] Sun Yilan, Zang Xiaofeng, Liu Yinghui, etal.Progress in materials selection for flexible electrochemical sensors[J].Journal of composite materials:1-11. https://doi.org/10.13801/j.cnki.fhclxb.20231205.002.

[13] Gao Ruilin, Wen Lirong, Guo Weisi.Advances in electrochemical promotion of

functionalization of unactivated C (SP ~ 3)-H[J]. Organic chemistry:1-16. http://kns.cnki.net/kcms/detail/31.1321.O6.20231130.1504.004.html.

[14] Li jiaming, Meng Xiaorong, Wu Zhenpeng. High stability LiAl0.1MN1.9O4 was used to extract lithium from electrochemical brine[J].Chemical Industry and engineering:1-12. https://doi.org/10.13353/j.issn.1004.9533.20230160.

[15] Hui Chenke, Yan Lingpeng, Yang Weipeng, etal. Progress in the application of graphene aerogel composites in electrochemical energy storage[J].Journal of composite materials:1-16. https://doi.org/10.13801/j.cnki.fhclxb.20231115.001.

[16] Yu Dazhao, Zhang Tong, Liu Qi. The corrosion deposition distribution of H62 copper alloy was studied based on the level set method[J]. Journal of Ordnance Equipment Engineering,2021,42(07):263-268.

[17] Zhang Han, Wang Yonglong, Zhang Bo, etal. Nitrogen-doped carbon nanotubes encapsulated with Ni-doped FEP nanoparticles were used as bifunctional electrocatalysts[J]. Science China(Materials),2023,66(12):4630-4638.

[18] Cao Zeyu, Zhang Xin'ai, Zhang Bo, etal. Study on electrocatalytic reduction of CO2 over MOF-based Ni-N-C catalyst regulated by Ni nanoparticles[J].Modern Chemical Industry:1-15. http://kns.cnki.net/kcms/detail/11.2172.TQ.20231129.1346.020.html.

[19] Zhang Shengyong, Jiang Ru, He yi, etal. Asymmetric catalytic synthesis of chiral drugs: opportunities and challenges[J].Journal of Air Force Medical University:1-19. http://kns.cnki.net/kcms/detail/61.1526.R.20231120.1306.004.html.

[20] Zhu Jing, He Huan, Jiang Xuefeng. Concepts and objectives in scientific research: Ericsson and the field of Enantioselective synthesis[J]. Chinese Journal of Chemical Education,2023,44(19):1-14. DOI:10.13884/j.1003-3807hxjy.2023090084.