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Innovative Reforms in Medicinal Chemistry Teaching: From Theory to Experiments

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Abstract: *Recent breakthroughs in life sciences technologies and artificial intelligence have significantly increased the demand for innovative and interdisciplinary pharmaceutical professionals. Traditional teaching models in medicinal chemistry are facing unprecedented challenges and require urgent reform and transformation. In order to meet the training goals and needs of pharmaceutical professionals and enhance the innovative thinking and scientific literacy of undergraduate students in pharmaceutical sciences, this study explores innovative reforms in the teaching model of medicinal chemistry, encompassing both theoretical instruction and laboratory experiments. The study focuses on the characteristics of the Medicinal Chemistry course, evaluates the current state of medicinal chemistry education, and explores the approaches for reforming both theoretical and experimental teaching in Medicinal Chemistry.*

Keywords: *Medicinal Chemistry, Innovative teaching, Literature reading, Computer-aided drug design, Sulfacetamide sodium, Pharmacological evaluation*

1. Introduction

Based on the discipline of chemistry, medicinal chemistry covers multiple subjects, including pharmacology, toxicology, pharmaceutics, pharmaceutical analysis, biology, and medicine, characterized by its strong interdisciplinary nature, complexity, and vast knowledge system [1]. As a discipline that relies on the integration of applied and basic sciences, medicinal chemistry plays a crucial role in drug discovery and development [2]. In recent years, disciplines such as molecular biology, structural biology, computer science, and information technology have made rapid advancements and achieved numerous breakthroughs, providing new directions and content for research in medicinal chemistry. Thanks to the application of cutting-edge technologies from multiple disciplines in new drug development, innovative drugs and their molecular mechanisms are continually being discovered and elucidated. A significant challenge in medicinal chemistry education is how to integrate fundamental theories with cutting-edge research findings and practical drug research within the limited teaching time. Our teaching team has innovated both the theoretical and experimental teaching models in medicinal chemistry, combining traditional knowledge with the latest scientific developments, linking theory with practice, and broadening the depth and scope of professional knowledge, thus laying a solid foundation for fostering the research mindset and innovative abilities of undergraduate pharmacy students.

2. Analysis of the Current State of Medicinal Chemistry Teaching

2.1 Current Status of Medicinal Chemistry Theoretical Course Teaching

The Medicinal Chemistry course covers 11 major categories, including antibiotics, antiviral drugs, sedative-hypnotics, antipsychotic drugs, non-steroidal anti-inflammatory drugs, gastrointestinal drugs, and antitumor agents. The broad scope of the curriculum places a substantial burden on students, which negatively affects their motivation to learn. The teaching of medicinal chemistry typically follows a line of representative chemical drugs, covering topics such as the discovery and development of drugs, chemical structures, naming, physical-chemical properties, drug synthesis methods, metabolism in the body, mechanisms of action, and structure-activity relationships (SAR). However, with the rapid advancements of life sciences and the continuous emergence of innovative drugs, the teaching of

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medicinal chemistry faces the challenge of keeping up with the latest developments and research in the field. For example, in 2024, the FDA approved 50 new drugs, 16 of which were biologics, including fusion proteins, monoclonal antibodies, and bispecific antibodies [3]. Among these, significant progress has been made in therapies for rare diseases, which have become a major area of focus. However, current medicinal chemistry theory teaching is mainly focused on chemical drugs, with limited coverage of emerging biologics, such as monoclonal antibodies, vaccines, gene therapies, cell therapies, peptides, and antibody-drug conjugates. This imbalance results in a curriculum that lacks both cutting-edge relevance and practical value.

2.2 Analysis of the Causes of Issues in Theoretical Courses

Upon analyzing the challenges in current medicinal chemistry theory teaching, several key causes can be identified: (1) Medicinal chemistry is characterized by strong interdisciplinary integration, complex and abstract content, and rapid knowledge updates, which pose significant challenges to effective course delivery; (2) Many universities face the issue of insufficient class hours for medicinal chemistry, making it difficult to cover advanced topics such as the drug discovery process, the latest research progress in drug development, and cutting-edge technologies in life sciences [4]; (3) Traditional teaching methods rely mainly on PowerPoint presentations or chalkboard explanations to cover the structure, physicochemical properties, synthesis methods, pharmacological effects, and molecular mechanisms of different drug molecules. Given the limited depth of knowledge, pharmacy undergraduates often memorize core content without truly understanding, leading to a lack of engagement and interest in learning, which negatively impacts teaching effectiveness.

2.3 Current Status of Medicinal Chemistry Experimental Course Teaching

In terms of experimental courses, most medicinal chemistry experiments in universities across the country still primarily focus on traditional chemical synthesis experiments, repeating the synthesis of classic drugs such as aspirin and acetaminophen [5, 6]. These syntheses are relatively simple and mainly involve synthesis and characterization. Such experimental content overlaps with organic chemistry and drug synthesis courses. Traditional medicinal chemistry experiments focus on the preparation of chemical drugs, training students in basic drug synthesis methods, reaction mechanisms, and structural identification, but rarely address pharmacological evaluation or SAR studies. Furthermore, medicinal chemistry is not solely a chemistry discipline but is deeply intertwined with life sciences. Purely focusing on drug synthesis fails to fully reflect the interdisciplinary nature of medicinal chemistry, which bridges chemistry and life sciences. Therefore, innovative reforms in the teaching model of both theoretical and experimental medicinal chemistry courses are inevitable.

2.4 Analysis of the Causes of Issues in Experimental Courses

The challenges in medicinal chemistry experimental teaching can be attributed to several factors: (1) Medicinal chemistry experiments require specialized equipment and biological reagents, which are relatively expensive. Some universities face issues with outdated equipment or insufficient resources, limiting the conduct of experiments such as pharmacological evaluation; (2) Drug development is a lengthy process involving multiple stages, such as drug discovery, design, synthesis, pharmacological evaluation, and safety assessment. Due to insufficient class hours, the integration of drug synthesis with biological experiments is challenging, which extends the experimental cycle and increases the teaching difficulty; (3) Medicinal chemistry, as a rapidly developing frontier subject in pharmacy, has experimental teaching content that lags behind, focusing mainly on synthesis skills and neglecting the students' innovation and comprehensive abilities.

3. Innovative Reform Methods for Medicinal Chemistry

3.1 Literature Reading

Medicinal chemistry, as a rapidly advancing frontier discipline within pharmacy, intersects with multiple other fields and encompasses a broad and diverse range of research topics. Given the limited professional knowledge base of undergraduate students, many lack both innovative thinking and scientific thinking when studying medicinal chemistry. This makes it challenging for them to grasp the

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key research hotspots and recent advancements in the field. Therefore, it is crucial for instructors to provide appropriate guidance and inspiration when selecting research topics.

In the context of training students in scientific literature reading related to medicinal chemistry, several potential research themes can be proposed, including: the latest advancements in specific drug classes, such as sedative-hypnotics and antibiotics; research on drugs targeting specific mechanisms, such as the study of angiotensin-converting enzyme inhibitors (ACEIs) and proton pump inhibitors (PPIs); investigations into the pharmacological properties of certain drugs or scaffold compounds, such as the discovery of new anti-inflammatory effects of β-lactam compounds; drug development focused on specific clinical diseases, such as COVID-19 or Parkinson's disease treatments; and the application of drug design strategies, including prodrug design, soft drug advancements, and innovative technologies in medicinal chemistry, such as Computer-Aided Drug Design (CADD), DNA-Encoded Library Screening (DEL), omics technologies, and combinatorial chemistry.

In practical teaching, many groups have integrated pressing clinical needs and societal issues into medicinal chemistry literature training, proposing research themes that address contemporary challenges. For instance, research themes include the use of CADD in the design of anti-COVID-19 drugs, the development of Alzheimer's disease therapeutics, the exploration of opioid addiction mechanisms, and the comparative potency and addictive properties of fentanyl versus morphine [7-9]. Other examples include understanding the binding mode of ibuprofen to cyclooxygenase-2 (COX-2) from a structural biology perspective and exploring the reasons behind the enhanced activity of the *S*-enantiomer [10]. This approach significantly enhances student engagement in scientific research and exemplifies a "student-centered" methodology. By reading literature on these topics, students gain the ability to analyze and address the scientific challenges in new drug development from various angles, allowing for in-depth exploration and critical reflection. Through literature reading, students gradually develop research ideas, fostering both their scientific thinking and innovative abilities.

3.2 Class Presentations

Before starting the literature reading practice, teachers need to train students in literature retrieval, management, and analysis skills, as well as introduce the strategies for reading scientific literature and the use of relevant software. Students should first be introduced to the use of various database resources, including both open-access and university library-subscribed databases. Common Chinese databases include CNKI, Wanfang, and VIP, while foreign databases include Web of Science, Wiley, Springer, American Chemical Society journals (ACS), Science, and the Cell series of journals. Students can search, analyze, and summarize relevant literature in these databases based on topics related to Medicinal Chemistry, and develop the ability to independently acquire new knowledge through the application of information technology and literature retrieval methods.

The specific implementation plan for scientific literature reading and sharing is as follows: undergraduate pharmacy students are divided into several learning groups, and each group selects an interesting research topic related to medicinal chemistry. Before the class, each group conducts literature retrieval, reading, and organization, selecting one member to present the literature in class. The group members collaborate, with the group leader overseeing the tasks of literature retrieval, reading and organization, extracting key findings, creating a PPT presentation, and delivering the presentation in class. The literature presentation should have a clear theme and cover content such as research background, representative drugs, mechanisms of action, and clinical applications. Introducing scientific literature reading and classroom presentations into medicinal chemistry courses is a student-centered teaching approach. This method not only helps expand the depth and breadth of the teaching content but also stimulates students' interest in learning and fosters innovative thinking.

3.3 Integrating Computer-Aided Drug Design into Theoretical Teaching

In recent years, the rapid development of computer science and artificial intelligence has had a profound impact on the field of medicinal chemistry, driving innovations in drug design, drug screening, and structure optimization, which significantly improves the efficiency of drug development. However, in traditional medicinal chemistry teaching, there is often a lack of integration with disciplines such as computer science, which means the course may not fully reflect the features and demands of modern medicinal chemistry. Moreover, relying solely on textual descriptions and two-dimensional images makes it difficult for students to intuitively understand the three-dimensional structure of compounds, the interaction mechanisms between drug molecules and receptors, and the structure-activity

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relationships of drugs. To address this issue, our teaching team has integrated software tools such as Autodock (a molecular docking software) and PyMOL (a molecular visualization tool) into the theoretical courses of medicinal chemistry. These tools allow instructors to demonstrate the three-dimensional structures of small molecules and use models such as ball-and-stick and cartoon representations to display protein structures. They can also highlight the key amino acids involved in the interaction between drugs and receptors. These software applications not only help students gain a deeper understanding of how drugs exert their effects but also vividly present the fascinating microscopic world of drugs, greatly enhancing students' interest and engagement.

By incorporating CADD into classroom teaching, the content delivery is enriched, providing students with a more intuitive and interactive learning experience. This approach enables students to master essential skills such as molecular modeling, drug-receptor interaction analysis, and structure-activity relationship studies, thus laying a solid foundation for future drug discovery and innovation.

4. Innovative Reform in Medicinal Chemistry Experimental Courses

4.1 Experimental Project—Synthesis and Antibacterial Activity Evaluation of Sulfacetamide Sodium as an Example

In the curriculum for pharmacy students, the "Experiments of Medicinal Chemistry" is usually offered in the second semester of the junior year. Prior to this, students have already completed courses like "Experiments of Inorganic and Analytical Chemistry", "Experiments of Organic Chemistry", "Experiments of Biochemistry", and "Experiments of Instrumental Analysis", which provide a solid foundation in organic synthesis, compound identification, and analysis. Therefore, the "Experiments of Medicinal Chemistry" can include comprehensive experiments that help students master scientific research methods and develop rigorous scientific literacy.

Sulfacetamide sodium is a broad-spectrum sulfonamide antibacterial drug that inhibits the growth of both Gram-positive and Gram-negative bacteria by interfering with their metabolic processes. Specifically, sulfacetamide sodium competes with para-aminobenzoic acid (PABA), a precursor of dihydrofolic acid, thereby blocking bacterial synthesis of dihydrofolic acid. Without sufficient dihydrofolic acid, bacteria cannot grow or reproduce, leading to inhibition of their growth or death. The synthesis of sulfacetamide sodium is a classic laboratory experiment involving acylation reactions, acid-base adjustments, and recrystallization for purification, and is widely used in medicinal chemistry teaching. However, the structure analysis and biological experiments related to sulfacetamide sodium are less commonly included. Therefore, this study introduces the structure analysis and antibacterial activity evaluation of sulfacetamide sodium to explore and research comprehensive experimental teaching that integrates medicinal chemistry theory with practice, further enhancing the quality of the experiment and stimulating student interest in scientific inquiry.

4.2 Literature Research to Determine the Synthesis Route

The synthesis of sulfacetamide sodium involves an acylation reaction, using sulfacetamide as the starting material, which reacts with acetylating agents (such as acetic anhydride) under alkaline conditions. The resulting sulfacetamide acyl is then reacted with sodium hydroxide to form sulfacetamide sodium. The types of by-products generated during the reaction are analyzed, and separation is achieved using differences in the physicochemical properties between the main product and impurities.

Recent studies have reported improved synthetic methods for sulfacetamide sodium. Factors such as solvents, reaction temperature, reaction time, pH control, and catalysts have been shown to affect the yield. Key aspects of research in medicinal chemistry experiments include monitoring the reaction process, analyzing by-products, purifying the product, and selecting green synthesis routes with high yields and minimal reagent usage. Before the experiment, pharmacy students are divided into pairs and asked to independently perform literature searches, gather relevant data, and compile various synthetic methods for sulfacetamide sodium.

4.3 Class Presentations

In the experimental session, each group presents the results of their literature research and compares different synthesis routes. The instructor organizes a discussion, summarizing the experimental methods, and finally selects the optimal synthesis route for sulfacetamide sodium from multiple perspectives,

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including green chemistry, economic feasibility, and operational convenience. Students then perform the synthesis and purification of sulfacetamide sodium according to the final experimental plan, monitoring the reaction progress using thin-layer chromatography.

4.4 Structure Characterization

Drug structure identification and analysis are crucial components of medicinal chemistry experiments. Traditional medicinal chemistry teaching tends to focus on the synthesis process, with less emphasis on structural analysis training. However, pharmacy students in their third year have already studied courses such as "Instrumental Analysis" and "Spectral Analysis", providing them with a foundation in compound structure analysis.

After completing the synthesis experiment, students first measure the melting point of the product to determine its purity, ensuring the accuracy of subsequent antibacterial activity assessments. They then use techniques such as nuclear magnetic resonance (^{1}H-NMR and ^{13}C-NMR), infrared spectroscopy (IR), and mass spectrometry to identify and analyze the chemical structure of sulfacetamide sodium. Since the experimental hours are limited and large instruments are more difficult to operate, the spectral data collection is done by the instructor. After the experiment, students analyze important spectra to confirm the molecular weight, functional groups, and bond types and locations, thereby confirming the chemical structure of the product. Integrating drug structure analysis into medicinal chemistry experimental teaching strengthens the connections between "Organic Chemistry", "Instrumental Analysis," "Spectral Analysis", and "Medicinal Chemistry", deepening students' understanding of basic theories and knowledge in chemistry.

4.5 Pharmacological Evaluation

The minimum inhibitory concentration (MIC) is an important indicator for evaluating the antibacterial activity of drugs against specific bacteria. A lower MIC value indicates stronger antibacterial activity. The MIC varies for different bacterial strains using the same drug. In this medicinal chemistry experiment, *Escherichia coli* was chosen as the test strain. In the pharmacological evaluation experiment, students use ciprofloxacin as the positive control drug and prepare different concentrations of sulfacetamide sodium and ciprofloxacin solutions. Each group then mixes 300 μL of the drug solution with 300 μL of diluted bacterial suspension, adds this mixture to a 96-well plate, and performs triplicate wells for each concentration. In the experiment, three control groups were set up: the blank control (containing only the blank medium), the negative control (containing only Escherichia coli suspension), and the positive control (a mixture of ciprofloxacin hydrochloride and bacterial suspension). After completing the setup, the plate is incubated at 37 °C for 24 hours, and the absorbance at 600 nm is measured using a microplate reader to determine the MIC.

Including the antibacterial activity evaluation of sulfacetamide sodium in the medicinal chemistry experimental course allows students to master the method for determining drug antibacterial activity and encourages them to integrate theoretical knowledge with practical application. Comprehensive experimental teaching helps students develop skills in experimental design and data analysis, enhancing their experimental ability and scientific literacy.

4.6 Course Assessment

The assessment components for this comprehensive Medicinal Chemistry experimental project include literature reading and presentation, pre-lab reports, experimental operations, data recording and analysis, lab reports, and reflection questions. The grading criteria for each component are as follows: (1) comprehensive literature reading, clear and logical presentation with emphasis on key points (20 points); (2) clear identification of the experimental objectives, preparation of the experimental principles and content, development of synthetic routes, analysis of the advantages and disadvantages of different routes, and proper citation of references (10 points); (3) proper setup of experimental apparatus, adherence to laboratory rules and regulations, and safe and standardized experimental operations (20 points); (4) careful observation of experimental phenomena, timely, accurate, and truthful recording of experimental data (10 points); (5) thorough completion of the experimental report, analysis of experimental data, consideration of problems encountered during the experiment, and summary of causes and countermeasures (20 points); and (6) structural analysis of the drug using infrared and nuclear magnetic resonance spectra, and completion of reflection questions (20 points).

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The assessment for this comprehensive Medicinal Chemistry experimental course evaluates students from multiple perspectives, including independent learning, experimental design, hands-on operations, and critical thinking. This approach replaces the traditional single-lab report grading method, offering a more holistic evaluation of students' innovative thinking and practical skills. It also stimulates their interest in learning and enthusiasm for research.

5. Significance of Innovative Reforms in Medicinal Chemistry Teaching

Traditional medicinal chemistry teaching is largely didactic, with students relying on rote memorization to complete theoretical courses. In experimental courses, students tend to follow experimental procedures without critical thinking or innovation. This approach places excessive emphasis on the delivery of fundamental knowledge and basic experimental skills, while neglecting the development of students' scientific thinking and innovative abilities. To address this gap, our teaching team has implemented innovative reforms in the medicinal chemistry curriculum. These reforms incorporate literature research, CADD, and class presentations into theoretical courses, while integrating literature reading, structural analysis, and pharmacological evaluation experiments into courses. This expansion of the curriculum enhances the depth and breadth of medicinal chemistry education and fosters student interest and creative thinking.

Through these reforms, the focus of medicinal chemistry teaching shifts from a teacher-centered to a student-centered model, promoting students' autonomous learning capabilities. Additionally, by engaging with scientific literature, students can acquire new knowledge beyond the textbook, stay informed about the latest developments in the field, and lay a solid foundation for future drug discovery or research careers. Moreover, in drug development, the identification and analysis of drug structures are indispensable. However, due to the high cost and complexity of analytical instruments like mass spectrometers and nuclear magnetic resonance, students often lack proficiency in interpreting organic compound spectra. Therefore, it is crucial to cultivate students' structural analysis skills in medicinal chemistry experiments. By integrating spectroscopic analysis theory with practical operations, students can enhance their structural analysis abilities and strengthen the connection between medicinal chemistry and other scientific disciplines. Finally, the inclusion of pharmacological evaluation experiments not only enriches the laboratory component of the medicinal chemistry curriculum but also helps students build a comprehensive knowledge system. This approach enables students to apply interdisciplinary theories and professional knowledge to solve problems encountered in drug development, thereby improving their overall competencies.

6. Conclusion

Medicinal chemistry is a pivotal discipline in the field of pharmacy, playing a crucial role in drug development and providing the theoretical and practical foundation for the development of innovative drugs. In recent years, thanks to the rapid advancements in life sciences, informatics, and computer science, the field of medicinal chemistry has witnessed the emergence of numerous new research methods and technologies. However, traditional medicinal chemistry teaching methods are relatively simplistic, with outdated content that fails to keep pace with emerging discoveries in life sciences and advancements in information technology. Moreover, experimental courses in medicinal chemistry predominantly focus on confirmatory and repetitive experiments, where students passively follow procedures and steps, limiting their opportunities for active learning and creativity. Therefore, comprehensive and innovative reforms to traditional medicinal chemistry teaching methods are crucial for improving educational quality, making this an important issue in undergraduate pharmacy education.

Our teaching team has introduced innovative teaching modes, such as research-based literature reading and CADD, into the medicinal chemistry curriculum, enriching the course content. In terms of experiment teaching, we have implemented a comprehensive medicinal chemistry experiment project using the synthesis and antimicrobial activity evaluation of sulfacetamide as an example. This project integrates knowledge from organic chemistry, instrumental analysis, spectroscopic analysis, medicinal chemistry, and chemical biology, offering rich, practice-oriented content. By combining theory and experiments, we have deepened students' understanding of interdisciplinary knowledge, enhanced their professional skills, and fostered innovative thinking. This approach contributes to the cultivation of versatile pharmacy professionals and the development of high-quality talent for the pharmaceutical industry.

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