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A Teaching Reform Pathway for Natural Medicinal Chemistry Based on Drug-Discovery Case Chains

Ran Bi* Yanli Chen
School of Pharmacy, Yancheng Teachers University, Yancheng 224007, China
* E-mail of the corresponding author: biran@yctu.edu.cn

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Abstract

Natural Medicinal Chemistry is a core undergraduate course for pharmaceutical engineering majors, connecting the fundamental chemistry of natural products with the practice of modern drug discovery. Conventional teaching is often structured around compound classes and research methods. Although this structure helps maintain disciplinary coherence, it may also leave knowledge points disconnected, reduce classic discovery cases to supplementary examples, and make it difficult for students to grasp the full process of natural product drug discovery. To address these issues, this study proposes a teaching reform pathway driven by drug-discovery case chains. By using representative cases as teaching carriers, the pathway links resource clues, structural features, physicochemical properties, extraction and separation strategies, bioactivity evidence, and development-oriented applications. These elements are further transformed into classroom questions and learning tasks, guiding students to understand the process from natural product discovery to drug development. Digital tools are incorporated to support case analysis and help students visualize structures, retrieve information, and organize evidence. Through pre-class preparation, guided in-class analysis, post-class learning outputs, and formative assessment, the design helps students move beyond memorizing isolated knowledge points toward process-oriented understanding and application-oriented analysis. The proposed approach offers a practical reference for content reconstruction and teaching implementation in related pharmacy courses.

Keywords: Natural Medicinal Chemistry; drug-discovery case chains; natural products; formative assessment

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1. Introduction

Natural products remain an important source of structural diversity and drug-discovery inspiration, and their derivatives continue to contribute substantially to the development of new therapeutic agents (Newman & Cragg 2020; Newman 2022). Recent advances in analytical technologies, genome mining, synthetic biology, and computational methods have further expanded natural product research from traditional isolation and identification to more integrated discovery strategies (Atanasov *et al.* 2021; Saldívar-González *et al.* 2022). These changes place new demands on the teaching of Natural Medicinal Chemistry at the undergraduate level. The course should not only introduce the chemical foundations of natural products, including structural classification, physicochemical properties, extraction and separation, and structure elucidation, but also help students understand how natural product resources are investigated, how active compounds are identified, and how research findings can be translated into drug-development opportunities.

In undergraduate pharmaceutical engineering programs, Natural Medicinal Chemistry is typically offered to third-year students. By this stage, students have usually completed foundational courses in organic chemistry, analytical chemistry, medicinal chemistry, and spectroscopic analysis. Nevertheless, they often struggle to integrate fragmented knowledge into a coherent understanding of natural product research. Textbooks generally organize course content according to compound classes and research methods, an arrangement that helps build a systematic knowledge framework. However, this arrangement may also widen the gap between classroom knowledge and the actual workflow of natural product drug discovery. In practice, natural product discovery rarely follows a simple linear route. Rather, it involves iterative interactions among resource investigation,

activity screening, target-compound tracking, structural identification, bioactivity validation, and development-oriented application.

Classic natural product cases, such as artemisinin, paclitaxel, bioactive constituents of Danshen, and huperzine A, offer representative entry points for linking natural product chemistry with drug discovery and pharmacological application (Weathers 2023; Sati *et al*. 2024; Tang & Zhao 2024; Suvaiv *et al*. 2025). However, when these cases are presented mainly as discovery histories or chapter-based examples, their potential to connect course knowledge and guide student learning remains underused. This limitation reflects the learning gap discussed above: students may remember representative compounds, structural features, and research methods, yet still struggle to understand how structure, properties, methods, bioactivity, and application are connected in the real process of natural product drug discovery. Therefore, classic cases should not only enrich teaching content, but also be reorganized into coherent case chains that support classroom questions, learning tasks, and formative assessment. On this basis, this study proposes a teaching reform pathway driven by drug-discovery case chains. Using classic drug-discovery cases as teaching carriers, this pathway integrates structure, properties, methods, bioactivity, and application into a process-oriented learning design. It also incorporates digital tool support, learning task design, and formative assessment to help students understand the process logic of natural product drug discovery.

2. Teaching Challenges in Natural Medicinal Chemistry

2.1 Fragmented Knowledge Organization in Chapter-Based Teaching

Natural Medicinal Chemistry covers a broad range of topics, including saccharides and glycosides, phenylpropanoids, quinones, flavonoids, terpenoids, triterpenoids and their glycosides, steroids and their glycosides, and alkaloids, as well as methodological topics such as extraction and separation, structure elucidation, bioactivity evaluation, and natural product development. Organizing teaching by compound class helps preserve the systematic structure of the discipline and enables students to establish a basic classification framework. However, this mode of organization may also lead students to view chapters as separate units and to treat structural types, physicochemical properties, extraction and separation methods, and bioactivity or application contexts as isolated knowledge points.

In teaching practice, students can often memorize the structural characteristics of a compound class or the basic principles of an extraction and separation method. When faced with a specific case, however, they often find it difficult to explain why a certain class of compounds is suited to a particular extraction strategy or how structural features influence separation behavior. This suggests a gap between memorizing individual knowledge points and understanding the drug-discovery process as an integrated whole (Tsekhmister 2023). For pharmaceutical engineering students, weak connections among structure, properties, methods, and applications may hinder their understanding of professional issues such as natural drug development, quality control, and process optimization.

2.2 Insufficient Pedagogical Use of Classic Cases

Classic drug-discovery cases are valuable teaching resources in Natural Medicinal Chemistry. However, in conventional teaching, they are often reduced to supplementary stories, introductory examples, or brief extensions of chapter content. Although this approach may increase students' interest, it does not fully support their integration of course knowledge or their understanding of the research logic behind natural product drug discovery. The key problem is not the absence of classic cases, but their insufficient transformation into structured learning tasks. When cases are not connected with classroom questions, tool-assisted analysis, learning outputs, and assessment activities, their pedagogical value cannot be fully realized (Zainal *et al*. 2024).

2.3 Limited Digital Support and Assessment Diversity

Digital resources are increasingly available in chemistry and pharmacy education, including structure drawing software, molecular visualization platforms, natural product databases, and literature retrieval systems, all of which can support undergraduate learning (Nothias *et al.* 2020; Bran *et al.* 2024; Ramos *et al.* 2025). In Natural Medicinal Chemistry, these tools should not be introduced merely to train students in software operation, but to help them understand structural features, physicochemical properties, extraction methods, bioactivity information, and the relationships among these elements. However, in conventional teaching, these tools are often used sporadically, and students have limited opportunities to apply them in case analysis or learning tasks.

At the same time, course assessment still relies largely on final examinations and regular assignments. This approach can evaluate students' mastery of basic concepts, but it is less effective in revealing whether they can connect knowledge points and understand the process logic of natural product drug discovery.

3. Course Design Based on Drug-Discovery Case Chains

3.1 Rationale for Drug-Discovery Case Chains

To address the challenges discussed above, this study proposes drug-discovery case chains as a framework for reorganizing classic natural product cases in Natural Medicinal Chemistry. The purpose is not simply to add more cases to classroom teaching, but to redefine the role of cases in the course. In a drug-discovery case chain, a representative natural drug or active compound serves as an organizing thread that structures classroom learning around a sequence of questions and tasks (Chen *et al.* 2025). In this way, the case is no longer a supplementary example of chapter content, but a teaching carrier that connects knowledge points, guides classroom inquiry, supports learning tasks, and helps students understand the logic of natural product drug discovery.

A case chain usually begins with a real discovery problem or a representative compound. Around this core, resource clues, structural features, physicochemical properties, extraction and separation, structure elucidation, bioactivity evaluation, and further development are organized into a continuous learning process. These elements are not presented as isolated knowledge points. Instead, they are connected through a sequence of questions and tasks, such as why a particular extraction method is suitable for a target compound, how structural features influence physicochemical properties, and how bioactivity evidence supports further development. Through this process, students can move from memorizing fragmented knowledge toward understanding the relationships among structure, properties, methods, bioactivity, and application.

For third-year undergraduate students, case-chain design should remain closely aligned with the core learning objectives of Natural Medicinal Chemistry. Digital tools can be introduced at appropriate points to support students' understanding rather than to increase operational complexity. Structure drawing software, molecular visualization tools, databases, and literature retrieval platforms can help students recognize key structural units, compare physicochemical properties, obtain compound information, and organize evidence for case analysis. Learning outputs, such as annotated structure diagrams, case-chain maps, process comparison tables, and compound information cards, make students' learning process visible and provide evidence for formative assessment. Therefore, drug-discovery case chains integrate case selection, question guidance, tool support, learning outputs, and feedback into a coherent and process-oriented teaching design.

3.2 Selection and Integration of Representative Cases

The selection of representative cases is a key step in implementing drug-discovery case chains. In this study, cases were selected according to three main considerations: their relevance to major course chapters, their ability to connect multiple knowledge points, and their suitability for third-year undergraduate learning. The aim is not to cover as many natural drug cases as possible, but to select cases that clearly support the learning of core course content. Each selected case should help students relate compound classes and structural features to physicochemical properties, extraction and separation strategies, structure elucidation, bioactivity evidence, and application contexts.

Based on the main content of the course, representative cases were arranged in chapters such as saccharides and glycosides, quinones, flavonoids, terpenoids and volatile oils, triterpenoids and their glycosides, and alkaloids. For example, polysaccharide cases can be used to connect glycosidic linkages, solubility, extraction methods, and quality evaluation. Flavonoid cases can support the teaching of scaffold recognition, phenolic hydroxyl groups, color reactions, and bioactivity discussion. Terpenoid cases such as artemisinin and paclitaxel can link structural features, extraction or supply strategies, structural modification, and drug development. In this way, each case is embedded in the corresponding chapter and reorganized into a focused case chain. The integration design of representative drug-discovery case chains in major chapters is shown in Table 1.

Table 1. Integration Design of Drug-Discovery Case Chains in Major Chapters

Chapter	Cases	Case-Chain Focus	Core Course Content	Learning Output
Saccharides and Glycosides	Ginseng polysaccharides; Astragalus polysaccharides	Bioactivity clues → polysaccharide extraction → structural characterization → bioactivity evaluation	Glycosidic linkages; polysaccharide structures; solubility; water extraction and alcohol precipitation	Extraction flowchart; compound information card
Quinones	Anthraquinones from Rheum; tanshinones from Danshen	Traditional purgative or circulation-promoting uses → quinone scaffold recognition → extraction and separation → quality-control analysis	Quinone scaffolds; acidity; redox properties; color reactions; chromatographic separation	Structural classification table; process comparison table
Flavonoids	Rutin; Ginkgo flavonoids; baicalin	Cardiovascular or anti-inflammatory activities → scaffold recognition → color reactions and identification tests → bioactivity discussion	Flavonoid scaffolds; phenolic hydroxyl groups; acidity; color reactions; extraction and separation	Annotated structure diagram; bioactivity evidence card
Terpenoids	Artemisinin; paclitaxel	Classic natural drug discovery → property analysis → extraction or supply strategy → structural modification	Terpenoid scaffolds; lipophilicity; stability; low-temperature extraction; semisynthesis; synthetic biology	Case-chain map; production pathway comparison table
Triterpenoids	Glycyrrhizic acid; ginsenosides; oleanolic acid	Active constituents→ saponin/aglycone comparison → extraction and transformation → bioactivity and application	Triterpenoid skeletons; saponin structures; surface active; acid hydrolysis; bioactivity	Structural comparison diagram; bioactivity summary
Alkaloids	Huperzine A; morphine; ephedrine	Active alkaloids→ basicity and salt formation → acid-base extraction → structural identification → target/application discussion	Basicity; salt formation; acid-base extraction; structural identification; bioactivity evaluation	Structural comparison diagram; separation strategy diagram

3.3 Designing a Representative Case Chain: Artemisinin as an Example

Artemisinin is one of the most representative cases in Natural Medicinal Chemistry. Its teaching value lies not only in demonstrating the contribution of Chinese scientists to natural product drug discovery, but also in connecting multiple knowledge points, including terpenoid structure, physicochemical properties, extraction methods, activity-guided tracking, structure elucidation, derivative development, and pharmaceutical application requirements. In this section, the artemisinin case is organized around a core question designed to stimulate student thinking: Why is conventional water decoction not an efficient way to obtain artemisinin-type antimalarial constituents?

Around this question, the artemisinin case chain is designed as five connected teaching nodes. The first node focuses on problem introduction. This node begins with the traditional medicinal use of *Artemisia annua* L. and guides students to consider how traditional experience suggested antimalarial activity and why water decoction may not be suitable for obtaining artemisinin-type active constituents. Through this introduction, students recognize that natural product drug discovery is not a simple repetition of traditional experience, but requires modern chemical methods to explain and verify the material basis of efficacy.

The second node focuses on structural feature recognition, including the sesquiterpene lactone structure of artemisinin, its peroxide bridge, lipophilicity, and stability. The learning task requires students to draw the structure of artemisinin using ChemDraw and label key structural units, including the lactone group and peroxide bridge. Through structural observation and annotation, students connect structural features with solubility, stability, and extraction-condition selection.

The third node focuses on extraction-method selection. On the basis of structural feature recognition, students further analyze why low-temperature organic solvent extraction is more suitable for artemisinin-type compounds. By linking lipophilicity, thermal stability, activity retention, solvent selection, and temperature control, students understand that extraction is not a fixed procedure, but a method determined by the properties of the target compound and the purpose of the study. The learning output of this node can be a written rationale for low-temperature extraction or a relationship diagram connecting structure, properties, and extraction method.

The fourth node focuses on structure elucidation and bioactivity evaluation. Natural product drug discovery

requires not only the isolation of target compounds but also reliable structure elucidation and bioactivity validation. This node is organized around questions such as how spectroscopic evidence can be used to confirm the structure of an isolated compound and how bioactivity evaluation can demonstrate its pharmacological significance. It helps students understand the continuous relationship among separation, structure elucidation, and activity validation.

The fifth node focuses on research extension. After basic case analysis, the artemisinin case is extended to modern drug development. Dihydroartemisinin, artemether, and artesunate are introduced to show how structural modification can improve solubility, stability, and clinical applicability. Combination therapy, drug resistance, and quality consistency are used to explain why natural product drugs still face requirements related to efficacy maintenance and quality control after entering clinical use. In addition, artemisinic acid biosynthesis, microbial cell factories, and semisynthetic production can be briefly introduced to show that modern natural product research has expanded from plant extraction to synthetic biology and green preparation. The learning output of this node can be an artemisinin development information card, with students required to verify the reliability of information sources.

Through this chain, the artemisinin case is transformed from a discovery-history story into a comprehensive teaching carrier. By completing annotated structure diagrams, case-chain maps, rationales for low-temperature extraction, and research-extension briefs, students can connect structural features with method selection, bioactivity validation, and development needs. This example shows how a classic case can be reorganized into a process-oriented learning pathway for Natural Medicinal Chemistry.

4. Teaching Implementation and Formative Assessment

4.1 Workflow of Case-Chain Teaching

Drug-discovery case-chain teaching can be implemented through four stages: pre-class preparation, in-class case analysis, post-class output development, and feedback-based improvement. In the pre-class stage, the teacher provides case background materials, representative structures, and preview questions through the learning platform, enabling students to identify the core problem of the case before class. Preview questions should be closely linked to classroom priorities, such as structural features of target compounds, differences in physicochemical properties, extraction-method selection, and bioactivity evaluation strategies. Tasks should be focused and manageable rather than overly broad or scattered.

The in-class stage is the core of case-chain teaching. Around the central case problem, the teacher guides students to analyze the relationships among resource clues, target compounds, structural features, physicochemical properties, extraction and separation, structure elucidation, bioactivity evaluation, and development-oriented application. Students may use ChemDraw to draw structures and label functional groups, molecular visualization tools to observe spatial structures, and databases to supplement information on compound sources, bioactivity, and application. For more advanced tools, such as molecular docking, molecular networking, and virtual simulation experiments, teacher demonstration may be more appropriate than requiring full student operation (McBane *et al.* 2023). These tools can help students understand structure-activity relationships, component recognition in complex systems, and modern research methods in natural product chemistry.

The post-class stage focuses on organizing and improving learning outputs. Based on classroom discussion and tool-assisted analysis, students complete tasks such as annotated structure diagrams, case-chain maps, process comparison tables, compound information cards, research-extension briefs, or reflective writing. Post-class tasks should focus on the core classroom questions and emphasize summarizing, revising, and refining the in-class analysis process. They should not be expanded into lengthy or loosely focused course papers.

In the feedback stage, the teacher uses students' learning outputs to evaluate learning outcomes, provide collective feedback on common problems, and offer individual guidance through the learning platform when necessary. Through the cycle of classroom analysis, learning output, teacher feedback, and output revision, case-chain teaching can be continuously refined.

As shown in Figure 1, the case-chain-based teaching reform framework consists of six components: teaching-problem identification, case-chain design, research-informed digital support, classroom implementation, learning outputs, and formative assessment. Current research and digital tools are embedded in case-chain design and classroom implementation, supporting structural recognition, property analysis, method selection, bioactivity understanding, and research extension. Formative assessment draws on students' learning outputs as evidence for teaching effectiveness and further informs adjustments to case difficulty, question-chain depth, tool-use level, and task requirements.

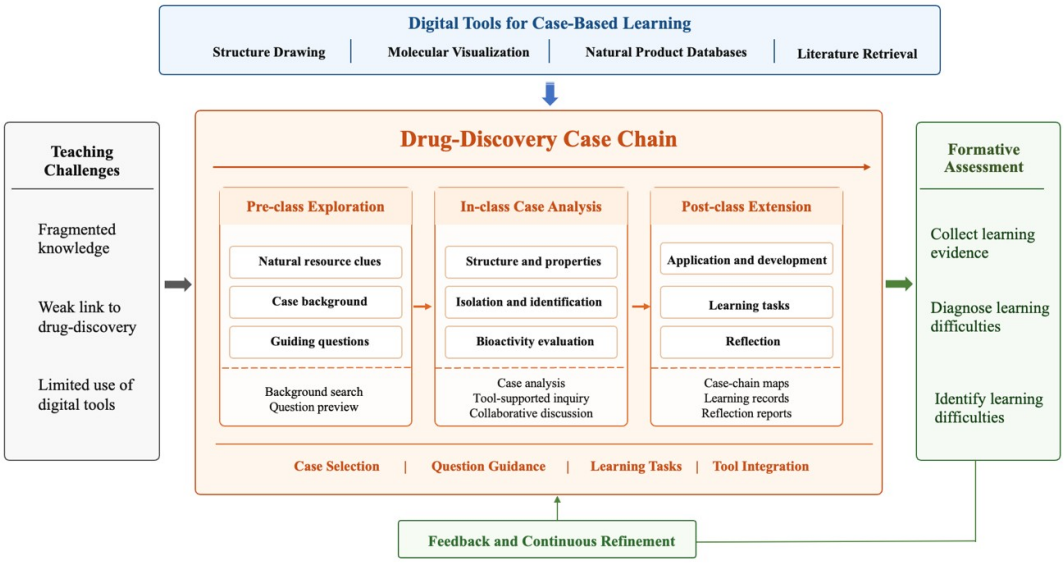

Figure 1. Case-Chain-Based Teaching Reform Framework

4.2 Formative Assessment and Continuous Improvement

Drug-discovery case-chain teaching emphasizes process understanding and application-oriented analysis. Therefore, assessment should not be limited to memory-based questions in final examinations (Sottiyotin *et al.* 2023). Formative assessment can be conducted across six dimensions: knowledge accuracy, logical linkage, method-selection ability, information retrieval and evidence organization, understanding of current research issues, and expression and reflection. Knowledge accuracy focuses on students' recognition of structural types, key functional groups, and physicochemical properties. Logical linkage and method-selection ability focus on whether students can explain the relationships among structure, properties, extraction and separation, bioactivity, and application. Information retrieval and evidence organization focus on whether students can use databases, literature retrieval, and AI-assisted tools to obtain and verify information. The dimension of current research understanding examines whether students can analyze topics such as resource sustainability, quality control, green preparation, molecular networking, and bioactivity prediction. Expression and reflection focus on whether students can clearly present their analysis and revise their previous understanding based on feedback.

Teachers can evaluate students' understanding of the case chain based on submitted case-chain maps, annotated structure diagrams, process comparison tables, compound information cards, and reflective writing. Based on these outputs, teachers can adjust case difficulty, question-chain depth, tool-use levels, and task requirements. Common problems can be addressed in subsequent classroom feedback, while individual difficulties can be addressed through the learning platform. Through the cycle of learning output, teacher feedback, output revision, and teaching optimization, both course content and teaching implementation can be continuously improved.

5. Conclusion

This paper addresses the mismatch between chapter-based knowledge instruction in Natural Medicinal Chemistry and the actual process of natural product drug discovery. To respond to this mismatch, a teaching reform pathway driven by drug-discovery case chains is proposed. Using classic discovery cases as teaching

carriers, this pathway connects course knowledge, case-based questions, digital tools, learning tasks, and formative assessment. It transforms classic cases from supplementary chapter materials into teaching threads that support content integration, research extension, and competency development.

Through case analysis, this design can guide students to understand connections among knowledge points, develop methodological awareness, and improve their ability to conduct application-oriented analysis. For undergraduate students majoring in pharmaceutical engineering, drug-discovery case chains can help reveal the internal connections within Natural Medicinal Chemistry and support the development of drug-discovery thinking, information retrieval skills, evidence organization skills, and professional learning interest. In future teaching practice, more evidence should be collected from classroom learning outputs, questionnaire feedback, and course assessment results. Such evidence will help further validate and optimize the teaching design and generate transferable insights for the reform of related pharmacy courses.

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