INSTRUCTIONAL DESIGN AND ASSESSMENT

Design and Implementation of a Laboratory-Based Drug Design and Synthesis Advanced Pharmacy Practice Experience

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Objective. To provide students with an opportunity to participate in medicinal chemistry research within the doctor of pharmacy (PharmD) curriculum.

Design. We designed and implemented a 3-course sequence in drug design or drug synthesis for pharmacy students consisting of a 1-month advanced elective followed by two 1-month research advanced pharmacy practice experiences (APPEs). To maximize student involvement, this 3-course sequence was offered to third-year and fourth-year students twice per calendar year.

Assessment. Students were evaluated based on their commitment to the project's success, productivity, and professionalism. Students also evaluated the course sequence using a 14-item course evaluation rubric. Student feedback was overwhelmingly positive. Students found the experience to be a valuable component of their pharmacy curriculum.

Conclusion. We successfully designed and implemented a 3-course research sequence that allows PharmD students in the traditional 4-year program to participate in drug design and synthesis research. Students report the sequence enhanced their critical-thinking and problem-solving skills and helped them develop as independent learners. Based on the success achieved with this sequence, efforts are underway to develop research APPEs in other areas of the pharmaceutical sciences.

Keywords: APPE, research, drug design, synthesis, medicinal chemistry

INTRODUCTION

Medicinal chemistry, a vital component of the pharmacy curriculum, provides students with a foundational understanding of the chemical basis of drug action.[1] This is typically accomplished by correlating the effects of a drug's physicochemical properties (logP, pK_a, acid/base properties, and water solubility) with their pharmacokinetic and consequent pharmacodynamic profile. Additionally, students learn that chemical characteristics and spatial arrangement of functional groups determine physicochemical properties and ultimately drug action through structure-activity relationships (SAR). To assist students in grasping medicinal chemistry concepts, a variety of interactive and active learning measures have been developed by medicinal chemistry faculty in addition to traditional classroom lectures.[2-16] A thorough understanding of the chemical basis of drug action allows pharmacy students to recommend safer and more effective alternative agents, identify potential drug-drug interactions, rationalize the basis for clinical recommendations, and ultimately solve clinical problems in order to improve patient care.

Students are also exposed to the vital role medicinal chemistry research plays in drug development efforts through a discussion of investigational agents or through individual faculty research presentations. Doctor of pharmacy students may find it difficult to participate in medicinal chemistry research as a result of the academic rigor of the pharmacy curriculum, time constraints, and a lack of structured research opportunities within the curriculum.

To provide PharmD students with an opportunity to participate in advanced study in medicinal chemistry research and to alleviate the time constraint on third-year and fourth-year students interested in drug design/discovery laboratory research, we incorporated a 3-course sequence, comprised of a one-month advanced elective followed by 2 one-month research-focused APPEs, into the curriculum. Standard 14 (Guideline 14.6) of the Accreditation Council for Pharmacy Education (ACPE) Standards,[17] which emphasizes the need to offer innovative elective APPE opportunities in a variety of areas including research, compelled us to move in this direction. Standards 2016 (Standards 10 and 13 and Appendix 2: Elective

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APPE) provide continued support for this model of research.[18]

In this paper we describe the structure of the advanced, lab-based elective course and APPEs and provide assessment data regarding the effectiveness of these courses in meeting faculty member and student expectations and needs.

DESIGN

Research is a key component of the pharmacy program at the Union University School of Pharmacy (UUSOP). Thus, we were interested in creating opportunities for PharmD students to learn critical research skills and participate in ongoing faculty-led efforts to design and synthesize new classes of pharmaceutical agents. One of the key challenges we faced was to determine how to diminish time constraints for students interested in participating in research. Laboratory-based research requires significant practice and skill in order to produce results worthy of dissemination. With this in mind, we elected to establish a period of 3 consecutive months for student research rather than a single month or multiple, nonconsecutive months.

In order to foster interest in research, academically strong, research-minded students were actively recruited during their first professional year and afforded opportunities to gain research experience during the summer months following their first and second professional (P1 and P2) years. Students assisted in research activities for 1 to 2 months. Students did not earn course credit, and no tuition was charged. Students were not compensated; however, they were granted pharmacy internship hours by the Tennessee Board of Pharmacy based on the number of research hours completed. Students who participated in summer research during their P1 and P2 years greatly improved their candidacy for the 3-course sequence. Additionally, APPE students with this experience would serve as mentors to new P1 and P2 summer interns.

For students completing the summer internship, we developed a 3-month sequence beginning with a 1-month, advanced laboratory-based elective course called Introduction to Medicinal Chemistry Research. During this course, students were taught techniques and principles pertaining to chemical synthesis and molecular modeling, along with general laboratory safety. After the elective course ended, students then completed 2 consecutive, 1-month APPEs, Advanced Drug Design and Synthesis I and II, during which students participated in various projects related to either drug design or synthesis (Table 1). Specific course objectives were mapped to the PharmD program's terminal outcomes. Overall, the summer internship followed by the elective and APPE sequence allowed students to gain a level of comfort with laboratory procedures and provided them with an opportunity to achieve significant results prior to graduation.

The medicinal chemistry elective course included training in chemical synthesis techniques and/or the basics of molecular modeling. Laboratory safety procedures and protocols were also introduced early in this elective course. Students worked closely with faculty members and research fellows to familiarize themselves with molecular modeling tools, drug design principles, and strategies associated with conducting a multi-step synthesis protocol. Students were trained to operate basic laboratory equipment including an automated purification system, microwave system, sample concentrator, infrared (IR) and ultraviolet (UV) spectrometer, ultra-high performance liquid chromatograph/mass spectrometer (UPLC/MS), and nuclear magnetic resonance (NMR) spectrometer. Upon completion of the course,

Table 1. Drug Design and Synthesis Elective Course and APPEs[a]

Course	Credit Hours	Course Objectives	UUSOP[b] Terminal Outcomes
Introduction to Medicinal Chemistry Research	2	Use computer-aided drug design techniques to develop novel therapeutic agents	Develop evidence-based pharmacotherapy plans Provide pharmaceutical care and disease state management Communicate effectively Function as an effective member of an interdisciplinary team
Advanced Drug Design and Synthesis I (APPE)	4	Use acquired laboratory skills to carry out synthesis of agents with therapeutic value	
Advanced Drug Design and Synthesis II (APPE)	4	Use acquired laboratory skills to purify small organic compounds Organize laboratory data and procedures in an electronic laboratory notebook Present research findings in a clear, well-organized fashion	

[a] APPE=advanced pharmacy practice experiences
[b] UUSOP=Union University School of Pharmacy

students began the APPEs with a focus on either drug design or synthesis and were adequately trained to initiate structure-based and/or ligand-based *de novo* design and synthesis protocols, with oversight from faculty members and postdoctoral fellows.

At UUSOP, students must complete 6 required and 4 elective APPEs. Each APPE is one calendar month in duration, and they begin in the spring semester of the third professional year. Students are allowed to complete up to 2 research-focused APPEs as electives. There is no difference in tuition for a research APPE vs a nonresearch APPE. During the drug design APPEs, students used a variety of molecular modeling tools and software and databases to perform structure-based *de novo* design of ligands or ligand-based virtual screening with a goal of identifying virtual lead compounds for chemical library synthesis.

Students completing the synthesis APPEs used their laboratory skills to synthesize and purify all compounds in these newly designed chemical libraries using solution-phase, parallel synthesis protocols and an automated purification system. Students characterized each synthesized compound using NMR, UV, IR, and mass spectrometry and then organized all data in an electronic laboratory notebook. Students learned valuable problem-solving skills as they executed new synthetic protocols and devised molecule-specific, purification methods. Students concentrating in either the drug design or drug synthesis also learned to organize data and present findings in a professional manner. At the conclusion of the 3-month course sequence, students had the option of presenting their results at a local or national pharmacy or chemistry meeting, depending on the specific project and the progress made. This decision was made by the faculty preceptor based on individual projects.

The choice of research project was critical to students' success in the drug synthesis/design APPEs and needed to be conducive to the skill set of a PharmD student. Drug design projects typically involved virtual screening and docking of compound libraries to identify "hits" for the development of small molecule chemical libraries. Once a library had been designed, the next phase involved synthesis. These projects involved solution phase, parallel, small molecule chemical library synthesis. Solution phase parallel synthesis is a technique that permits students to conduct multiple synthetic reactions at one time using identical or similar reaction conditions with a variety of starting materials to produce a number of structurally related compounds (chemical library). Prior to the start of each APPE, a library or part of a library was designed and the synthetic methodology elucidated. Having this work completed prior to the APPE allowed students to focus on a select group of molecules and solve any related synthetic issues that may arise. They learned how to monitor reactions by thin layer chromatography or mass spectrometry and how to work up reactions and purify and characterize final products. A representative library synthesis is shown below (Figure 1). A specific example is shown in Figure 2, along with representative yields.

During the 3-month sequence, students spent a minimum of 360 hours in the laboratory working on specific projects. The 3-course sequence was offered twice per year to accommodate student and faculty research interests and needs. We instituted an application process to help identify the most qualified students because only a limited number of students can be accommodated in research APPEs each year. Selection criteria included PharmD program grade point average (GPA), prior research experience, undergraduate science GPA, and performance in medicinal chemistry courses. As student interest increases, we have the option of adding an offering of the sequence. To date, 7 students have completed this research sequence with others scheduled to do so.

As with all the APPEs in the curriculum, both preceptors and students provide feedback by completing evaluations. Students were evaluated based on the criteria in Table 2 in order to determine course grades. Expectations were clearly delineated prior to the start of the sequence to ensure students were aware of how they would be evaluated and how their course grades would be determined. Establishing and discussing course expectations worked well and helped encourage students to work diligently in the laboratory each day. Students were also encouraged to self-assess their performance using the same preceptor evaluation rubric as indicated in Table 2.

Likewise, students were given the opportunity to evaluate the 3-course sequence using a 14-question rubric to provide feedback for course modification and improvement to meet their needs and those of faculty preceptors. Table 3 provides a summary of assessment data collected thus far from all students participating in the research courses. This work was approved by the Union University Institutional Review Board.

EVALUATION AND ASSESSMENT

Seven students completed the sequence over the past 2 years. Evidence of student learning was demonstrated by their participation in the elective course and APPEs resulting in significant research achievements within a short timeframe. Notably, student efforts resulted in the following: molecular modeling of 2 anti-infective target proteins; structure-based, *de novo* design of a chemical library of potential, small-molecule protein inhibitors;

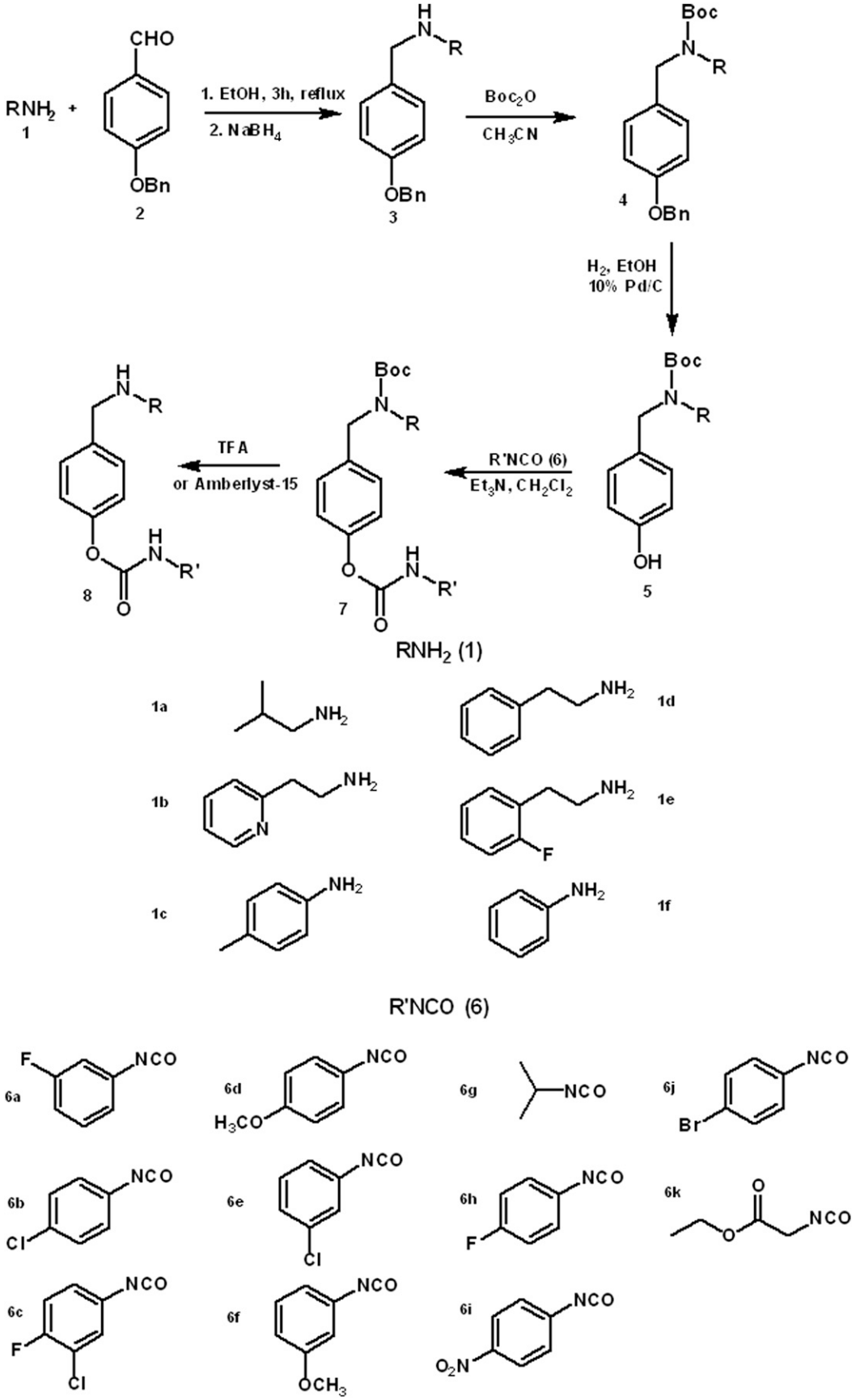

Figure 1: Example of solution-phase parallel synthesis conducted by student researchers.

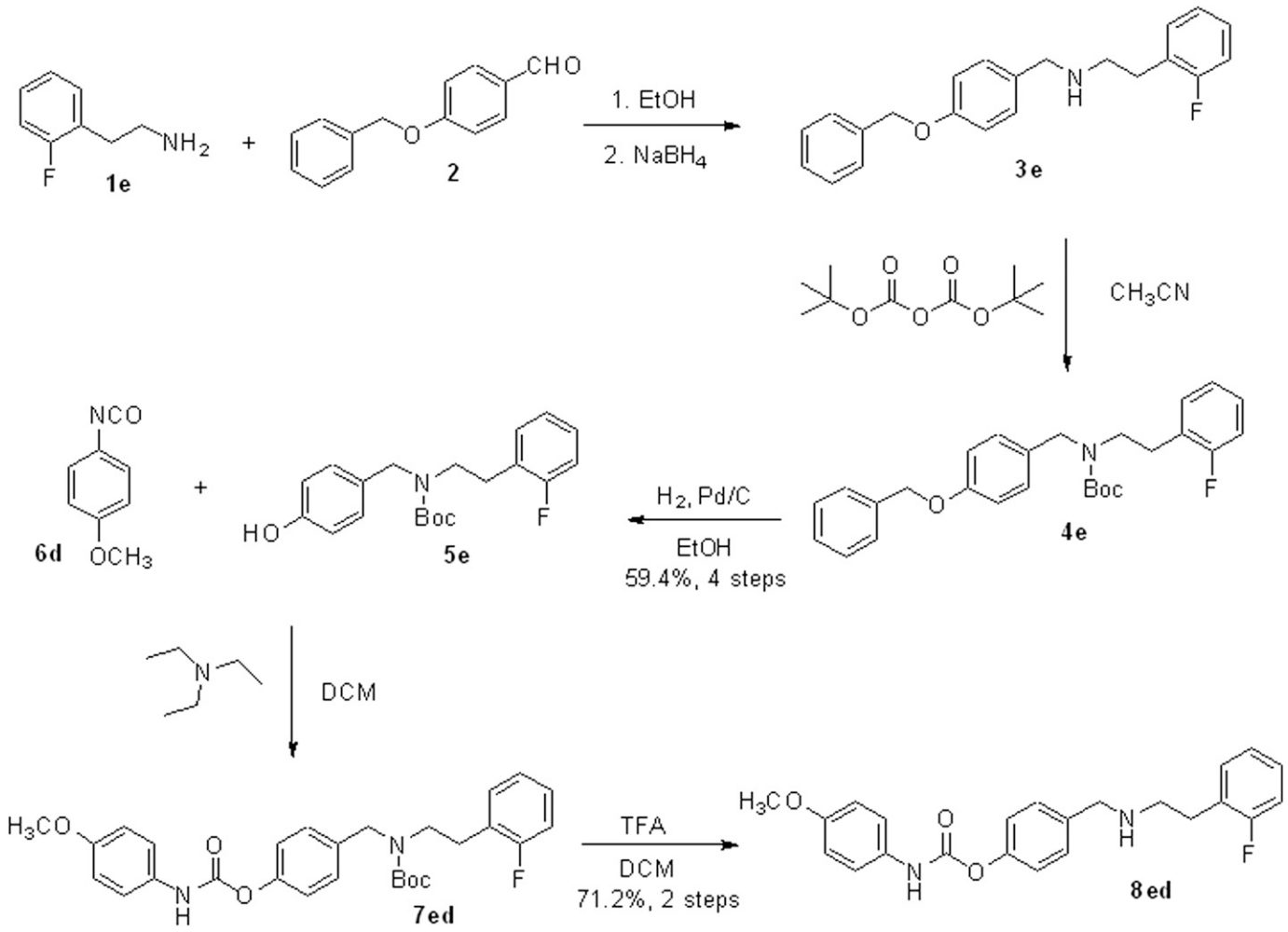

Figure 2. Example of synthesis of carbamate with representative yields conducted by student researchers

virtual screening for potential, small molecule inhibitors of an anti-infective protein; multi-step chemical library synthesis, purification, and full characterization of novel ligands; multiple poster presentations at university research symposia and local pharmacy meetings; a keynote presentation at a local meeting of the American Chemical Society; and incorporation of undergraduate research students into the pharmacy research program.

Table 3 contains feedback from students completing the course sequence. Although a small sample size, 86% of those participating agreed that the research APPEs were valuable and would recommend the practice experiences to their classmates. This type of feedback has been instrumental in furthering recruitment efforts within the department.

DISCUSSION

In the course of completing the sequence outlined above, students were given the opportunity to experience the benefits of conducting laboratory research and the challenges of doing so. For instance, they learned well thought-out plans often prove to be difficult to execute for a variety of reasons. These routine setbacks provide valuable teaching and problem-solving opportunities for students as they work with faculty members to devise plausible or practical solutions.

The establishment within a pharmacy curriculum of the research APPEs described here requires firm commitment from the school and from faculty members directly involved. Prior to each APPE, faculty members or postdoctoral fellows must select a library of compounds to be synthesized, and specific synthetic conditions must be delineated. During the APPEs, faculty members work closely with students to teach techniques and to ensure safety in the laboratory. Time commitments for faculty members depend heavily upon the experience of individual students. For this reason, the recruitment and training of students early in the curriculum is critical. While

Table 2. Preceptor Evaluation of Student Based on A, B, C, F Grading Scale

Evaluation Rubric
1. Ability to work as an effective member of a team:
Listens to others with attention
Communicates effectively with peers
Completes assigned work in a timely manner
Provides feedback to peers in a respectful manner
Takes the initiative in organizing team meetings
Attends team meetings on time
2. Ability to work independently and follow directions:
Follows procedures accurately
Completes training in a timely manner
Prepares for discussions appropriately
Demonstrates attention to detail
Uses drug design software and instrumentation efficiently
Demonstrates initiative and the desire to exceed expectations
Demonstrates a desire to work independently
3. Overall commitment to the project's success in terms of effort and time:
Demonstrates an interest to learn
Continuously self-evaluates and works to improve professional knowledge and skills
Accurately and concisely documents research activities
4. Ability to effectively collect, analyze, and accurately evaluate research data:
Applies critical-thinking and problem-solving skills to make rational decisions
Generates credible hypotheses for solving research problems
Critically analyzes design, methodology, results, and conclusions of published literature
Responds to questions clearly and concisely while citing appropriate sources
Creates well written, clear, and comprehensive research methodology protocols and reports
Collects relevant literature
Identifies avenues for intervention, ongoing research (advantages and disadvantages)
5. Function with professionalism in a research setting:
Demonstrates punctuality; arrives on time, is prepared
Demonstrates dependability, accountability, sense of duty, willingness to learn, positive attitude
Demonstrates a respect for and diligently follows safety protocols
Demonstrates respect for others, research facilities, and policies
Graciously receives feedback and seeks to improve performance
Exhibits professional, courteous, and respectful behavior
Accepts responsibility for assigned work and completes assignments on time
6. Ability to effectively communicate research findings:
Communicates effectively to peers and preceptors
Writes comprehensive and clear research protocols/lab reports with appropriate references
7. Peruses/interprets relevant literature, identifies specific research objectives to successfully accomplish research goals:
Discusses disease pathophysiology/biochemistry
Identifies avenues for intervention, ongoing research (advantages and disadvantages)
Identifies plausible objectives for accomplishing research goals

conducting research APPEs requires significant time commitment from faculty members, the commitment is typical for laboratory research.

Faculty members should consider possible limitations prior to starting APPEs in drug synthesis. As indicated above, certain synthetic projects are conducive to pharmacy APPEs while others are not. Parallel synthesis (solution or solid-phase) is easily amenable to pharmacy because it allows students to synthesize a large number of compounds in a small number of synthetic steps. Synthetic methodology projects are also options. Total synthesis projects would likely not be an option for this design because the average student would not possess the skill set or knowledge necessary for it. Importantly, projects should be designed to fit the skill set of the individual student so that a safe working environment is maintained. Thus, for safety reasons, PharmD students are not permitted to handle certain highly reactive re-

Table 3. Course Evaluation from Students Completing the 3-Course Sequence in Research

	Response[a]					
Survey Question	**1**	**2**	**3**	**4**	**5**	**Mean**
1. The level of difficulty of this course was appropriate for my skills and abilities.			1		6	4.7
2. The primary literature readings during the course were valuable.				2	5	4.7
3. The work assigned was reasonable for the course format and duration.					7	5.0
4. The course equipped me to meet future demands in the practice of pharmacy.			1	1	4	4.4[b]
5. The interactions and the discussions with the instructor were valuable.					7	5.0
6. The instructor reviewed the goals, objectives, and assignments at the beginning of the course.					7	5.0
7. The instructor exemplified the qualities and characteristics of what a researcher should be.					7	5.0
8. The instructor took an active interest in me and my learning experience.					7	5.0
9. The instructor coached me and facilitated my work and learning.			1		6	4.7
10. Instructor feedback was given in a constructive and nondemeaning manner.					7	5.0
11. Instructor feedback helped me improve my knowledge and skills.					7	5.0
12. The instructor answered my questions or directed me where to find answers.					7	5.0
13. The instructor asked questions that challenged me and helped me gain a greater depth of knowledge.				2	5	4.8
14. I would recommend this course to a classmate or undergraduate student.			1		6	4.7

[a] 5=strongly agree; 4=agree; 3=neutral; 2=disagree; 1=strongly disagree
[b] one student responded "not applicable"

agents including organolithiums. Transfers involving these reagents are conducted by faculty members or postdoctoral fellows.

CONCLUSION

Through participation in medicinal chemistry research, pharmacy students benefit from opportunities to develop, refine, and improve their critical-thinking and problem-solving skills while working with peers, postdoctoral fellows and faculty members on a variety of drug discovery projects. Medicinal chemistry research APPEs are now an integral part of the UUSOP experiential curriculum and offer students the opportunity to participate in drug discovery efforts, learn the valuable skills of problem solving, research planning, execution, organization, and dissemination of data. The research APPEs in this 3-course medicinal chemistry sequence provided students with an experience of pharmacy not routinely available in a traditional curriculum, helped strengthen their CVs, and made them stand out among their peers, especially with regard to residency placement. We are now in the planning stages of adding additional APPEs to the curriculum in the areas of pharmacology, pharmacometrics, and pharmaceutics research.

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