WEBER STATE UNIVERSITY

Blueprints Before Bricks:
The impact of early and intentional molecular modeling on project outcomes in a Medicinal Chemistry CURE

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Medicinal Chemistry CURE

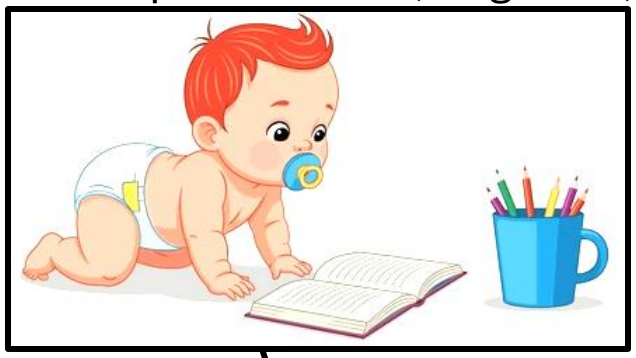
Goal of the course:

Designing a Better Drug through Computer-Aided Drug Design

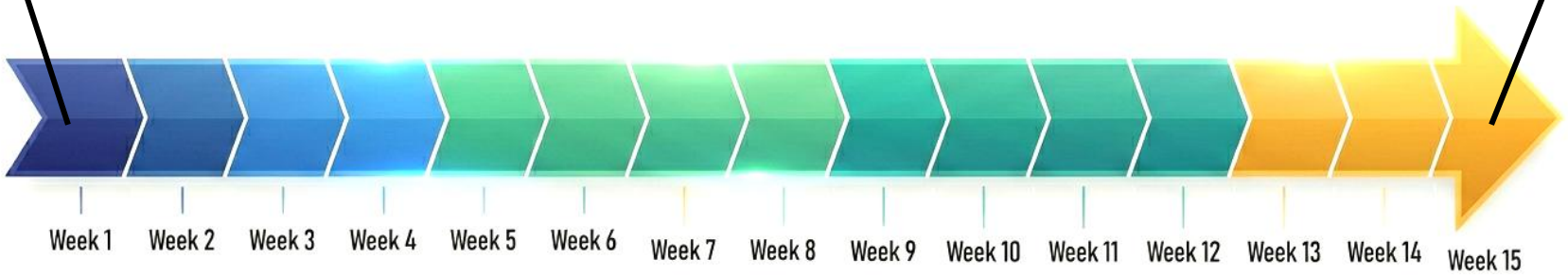
The goal of this project is to design a better drug molecule building upon foundational medicinal chemistry concepts learned over the course of the semester. You will select a medicinal chemistry topic of your choice, research the literature for relevant background information, identify a medicinal chemistry 'problem' in the literature, propose a solution for this problem based on foundational medicinal chemistry concepts, analyze your solution based on computer aided drug design (CADD) techniques, and report your results. For this project, you will demonstrate mastery of ALL of the CRE outcomes and at least 3 of the following specific learning outcomes, must include (#3, docking):

Medicinal Chemistry CURE

Level: Undergrads, Mostly seniors
Pre-reqs: Biochem I, Organic I, etc.



WSU research symposium



Designing a Better Drug through Computer-Aided Drug Design

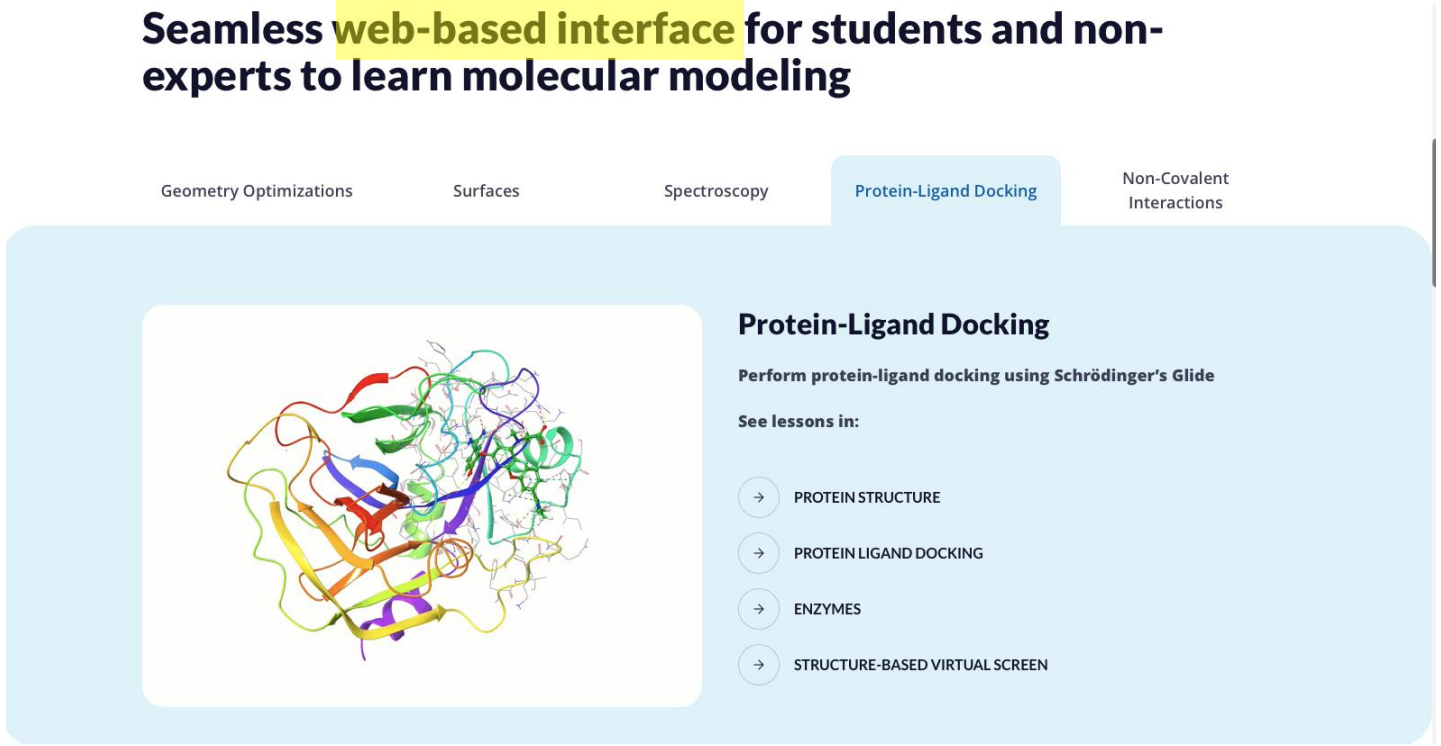
Medicinal Chemistry CURE: CADD Accessibility

From student evaluations Fall 2021:

“The only way to see if it (the project idea) actually works is to run it through a series of computer programs that are ancient and are never guaranteed to work unless you're a computer scientist.”

Medicinal Chemistry CURE: CADD Accessibility

Teaching with Schrödinger (TwS)



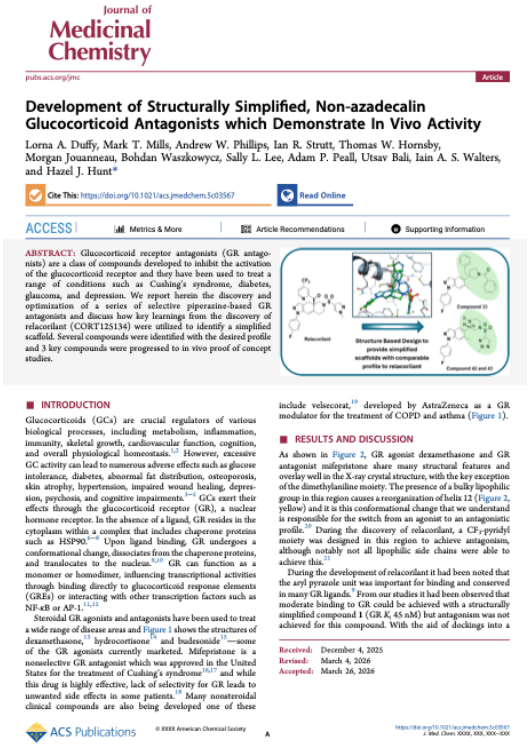
From student evaluations Fall 2025:

"I thought everything was fun and helpful and well thought out."

While TwS is not free, I've been able to get a grant from our Office of Undergraduate Research to support my CURE (always worthwhile to look for these opportunities)

Medicinal Chemistry CURE : Technical Literacy

Understanding the “Language” and Navigating Programs



Journal of Medicinal Chemistry

pubs.acs.org/jmc

Article

Development of Structurally Simplified, Non-azadecalin Glucocorticoid Antagonists which Demonstrate In Vivo Activity

Lorna A. Duffy, Mark T. Mills, Andrew W. Phillips, Ian R. Strutt, Thomas W. Hornsby, Morgan Jouanneau, Bohdan Waszkowycz, Sally L. Lee, Adam P. Peall, Utsav Bali, Iain A. S. Walters, and Hazel J. Hunt*

Cite This: https://doi.org/10.1021/acs.jmedchem.5c03567 Read Online

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ABSTRACT: Glucocorticoid receptor antagonists (GR antagonists) are a class of compounds developed to inhibit the activation of the glucocorticoid receptor and they have been used to treat a range of conditions such as Cushing's syndrome, diabetes, glaucoma, and depression. We report herein the discovery and optimization of a series of selective piperazine-based GR antagonists and discuss how key learnings from the discovery of relacorilant (CORT125134) were utilized to identify a simplified scaffold. Several compounds were identified with the desired profile and 3 key compounds were progressed to in vivo proof of concept studies.

■ INTRODUCTION

Glucocorticoids (GCs) are crucial regulators of various biological processes, including metabolism, inflammation, immunity, skeletal growth, cardiovascular function, cognition, and overall physiological homeostasis.[1,2] However, excessive GC activity can lead to numerous adverse effects such as glucose intolerance, diabetes, abnormal fat distribution, osteoporosis, skin atrophy, hypertension, impaired wound healing, depression, psychosis, and cognitive impairments.[3−7] GCs exert their effects through the glucocorticoid receptor (GR), a nuclear hormone receptor. In the absence of a ligand, GR resides in the cytoplasm within a complex that includes chaperone proteins such as HSP90.[8−10] Upon ligand binding, GR undergoes a conformational change, dissociates from the chaperone proteins, and translocates to the nucleus.[8,10] GR can function as a monomer or homodimer, influencing transcriptional activities through binding directly to glucocorticoid response elements (GREs) or interacting with other transcription factors such as NF-κB or AP-1.[11,12]

Steroidal GR agonists and antagonists have been used to treat a wide range of disease areas and Figure 1 shows the structures of dexamethasone,[13] hydrocortisone[14] and budesonide[15]—some of the GR agonists currently marketed. Mifepristone is a nonselective GR antagonist which was approved in the United States for the treatment of Cushing's syndrome[16,17] and while this drug is highly effective, lack of selectivity for GR leads to unwanted side effects in some patients.[18] Many nonsteroidal clinical compounds are also being developed one of these include velsecorat,[19] developed by AstraZeneca as a GR modulator for the treatment of COPD and asthma (Figure 1).

■ RESULTS AND DISCUSSION

As shown in Figure 2, GR agonist dexamethasone and GR antagonist mifepristone share many structural features and overlay well in the X-ray crystal structure, with the key exception of the dimethylaniline moiety. The presence of a bulky lipophilic group in this region causes a reorganization of helix 12 (Figure 2, yellow) and it is this conformational change that we understand is responsible for the switch from an agonist to an antagonistic profile.[20] During the discovery of relacorilant, a CF_3-pyridyl moiety was designed in this region to achieve antagonism, although notably not all lipophilic side chains were able to achieve this.[21]

During the development of relacorilant it had been noted that the aryl pyrazole unit was important for binding and conserved in many GR ligands.[5] From our studies it had been observed that moderate binding to GR could be achieved with a structurally simplified compound 1 (GR K_i 45 nM) but antagonism was not achieved for this compound. With the aid of dockings into a

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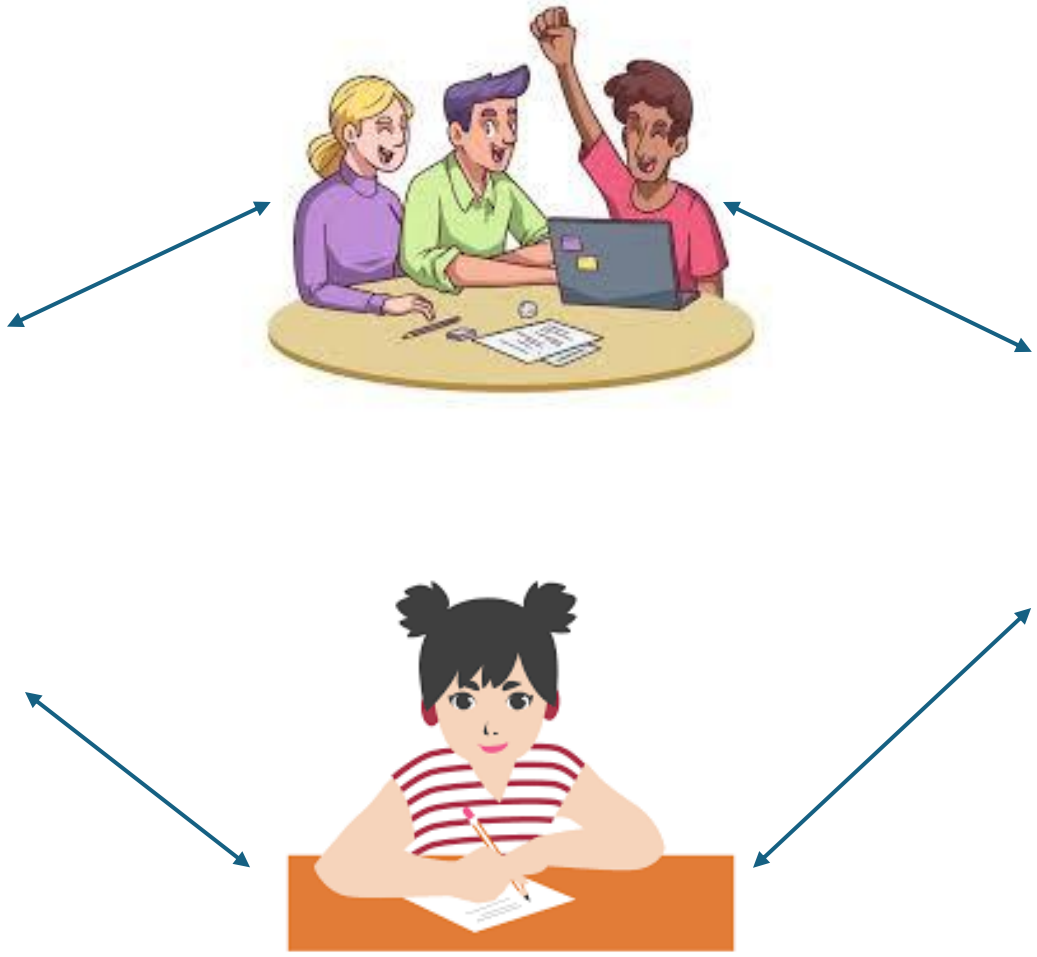
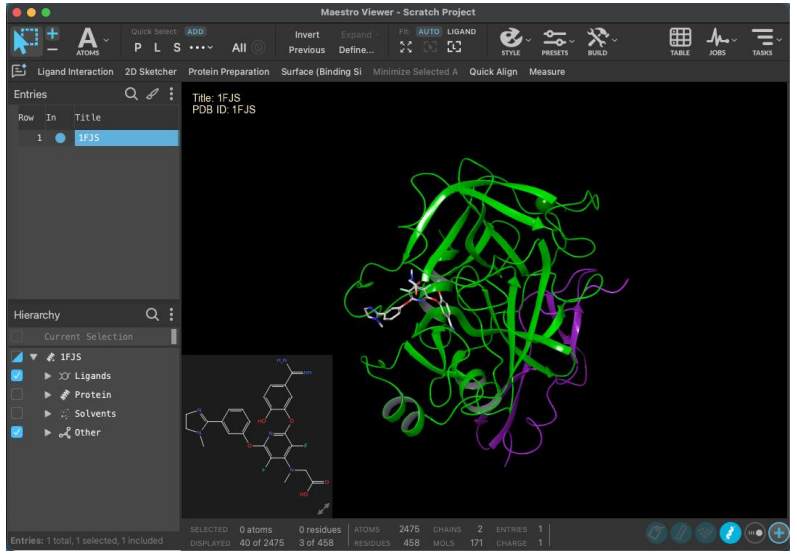
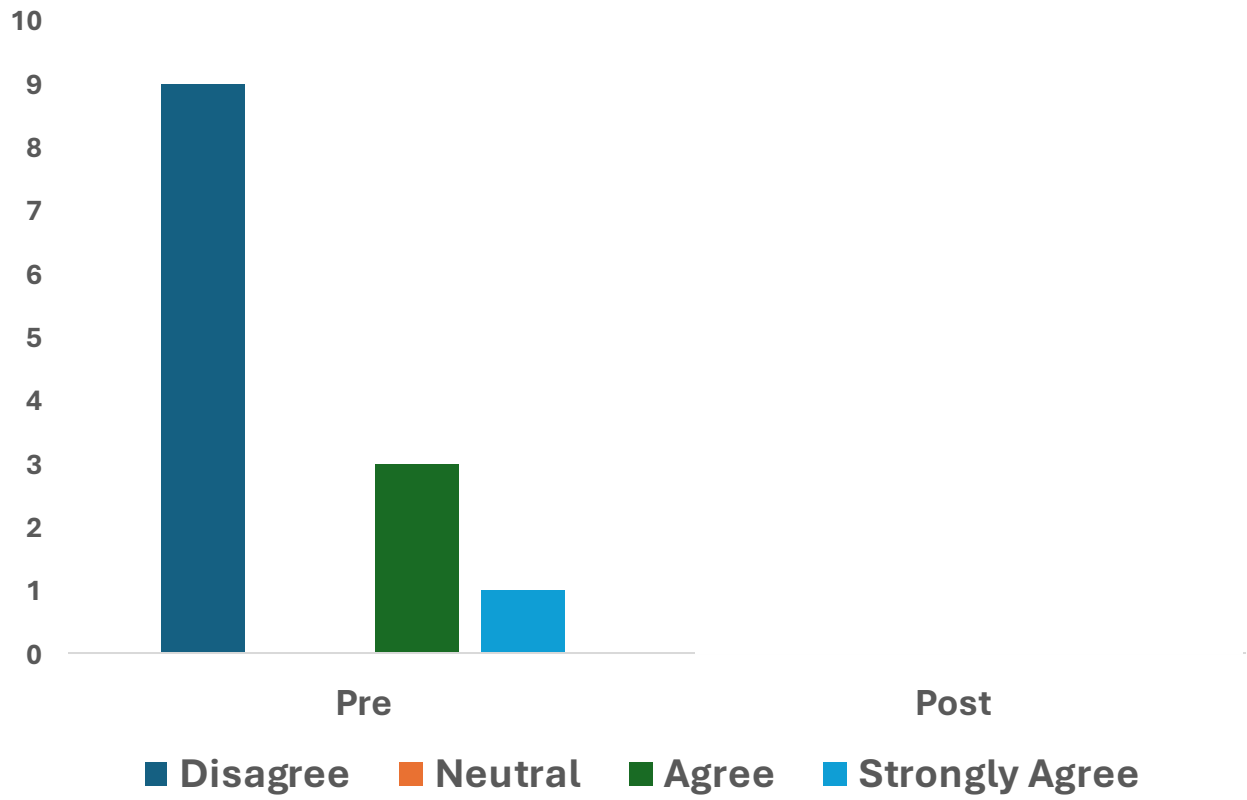
ACS Publications





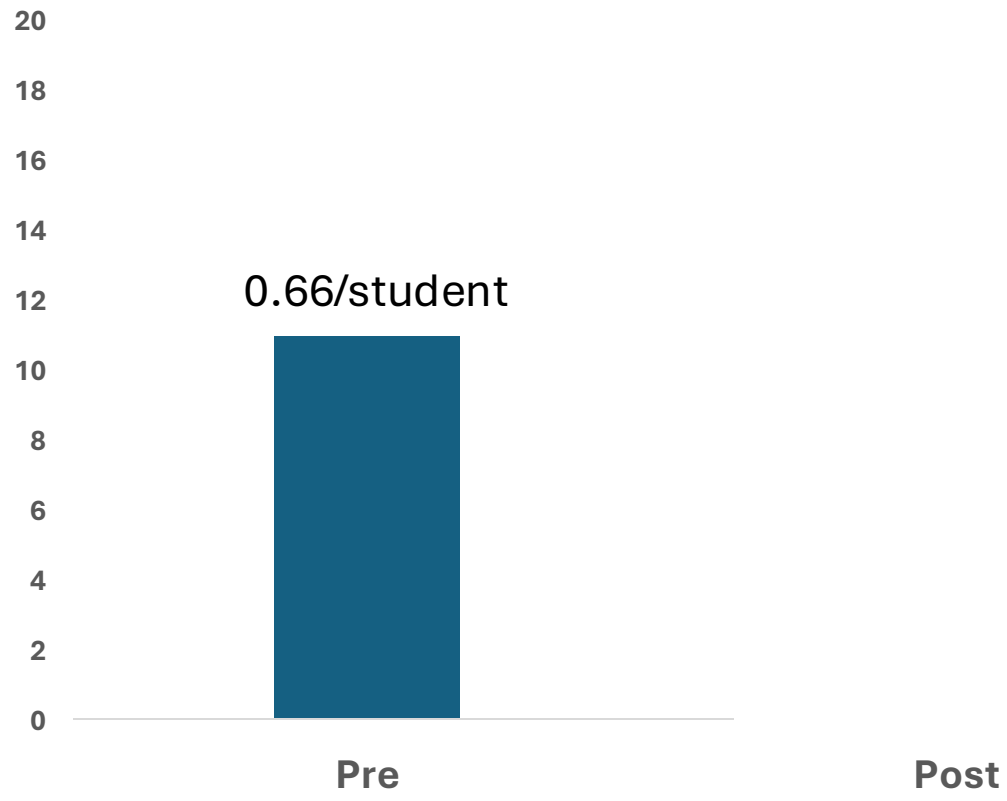
Medicinal Chemistry CURE : Technical Literacy

I am familiar with the major steps involved in medicinal chemistry research.



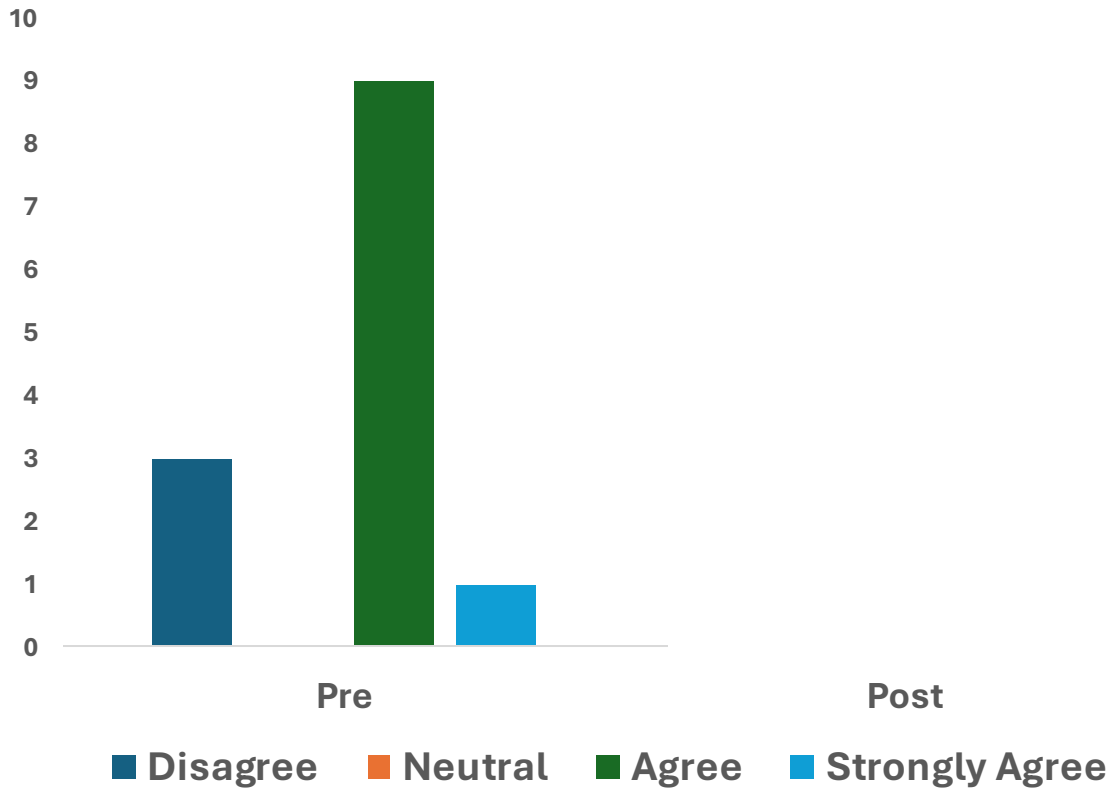
Medicinal Chemistry CURE : Technical Literacy

List two types of experiments or approaches commonly used in medicinal chemistry research.

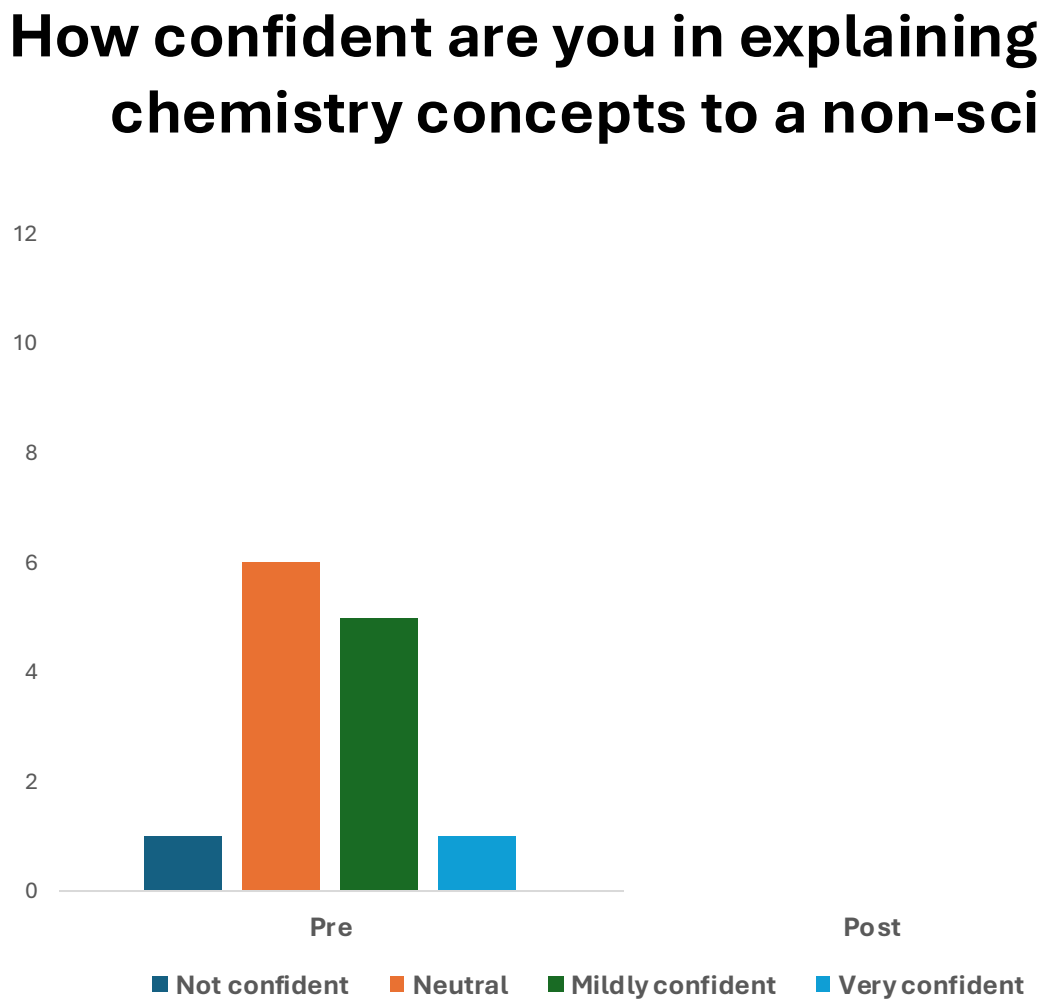


Medicinal Chemistry CURE : Technical Literacy

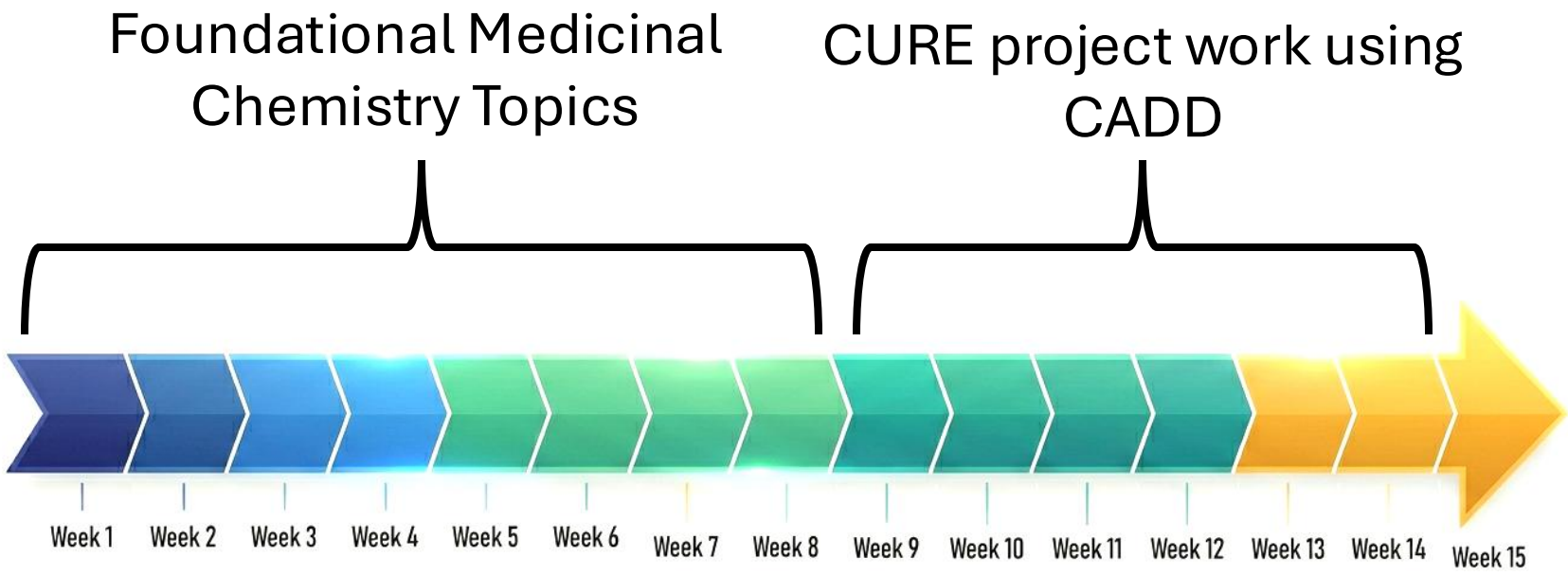
I know strategies to make complex science, such as medicinal chemistry, understandable to non-experts.



Medicinal Chemistry CURE : Technical Literacy



Medicinal Chemistry CURE : Timing

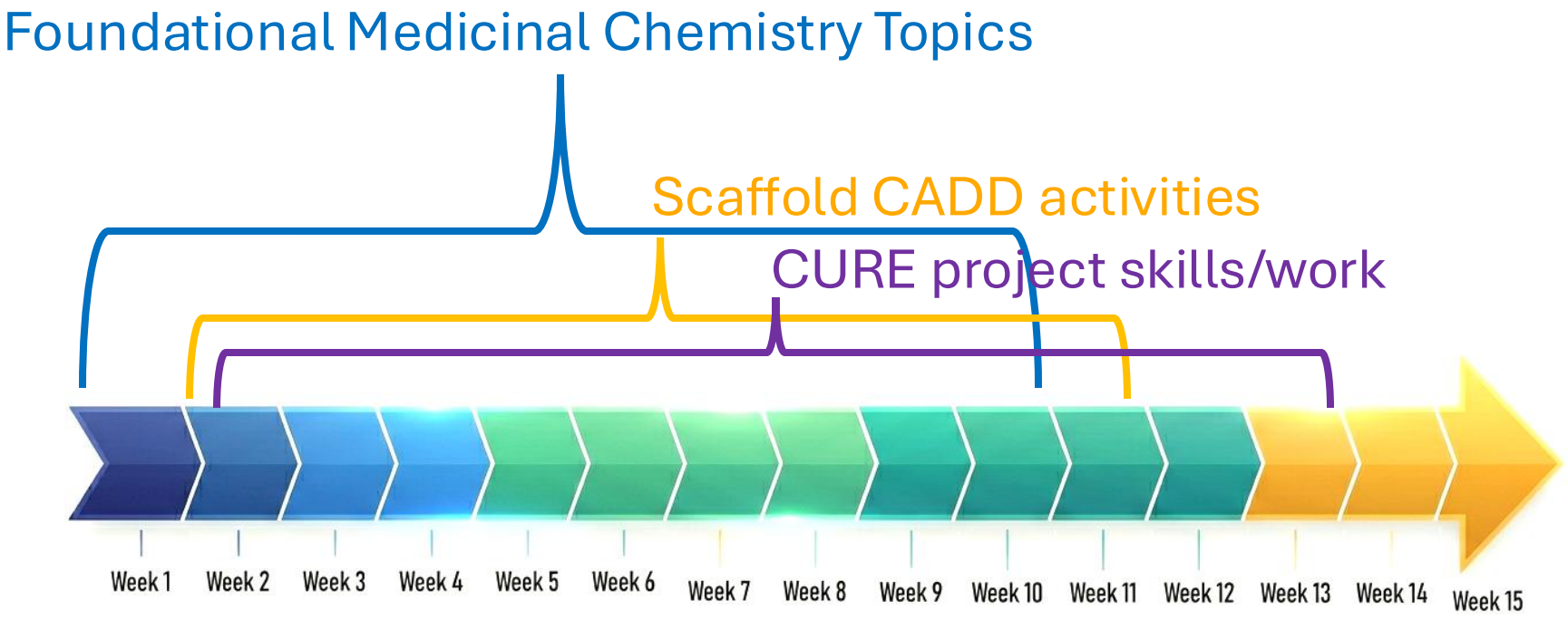


From student evaluations Fall 2021:

"I wish that we started working on the final project at the beginning of the semester to work out all the kinks in programs we'd be using as well and recognize concept we don't fully understand for the project."

"I just felt crunched for time. I could have started planning sooner, but the topics need to be taught first to even understand what the project is focusing on."

Medicinal Chemistry CURE : Early and Often

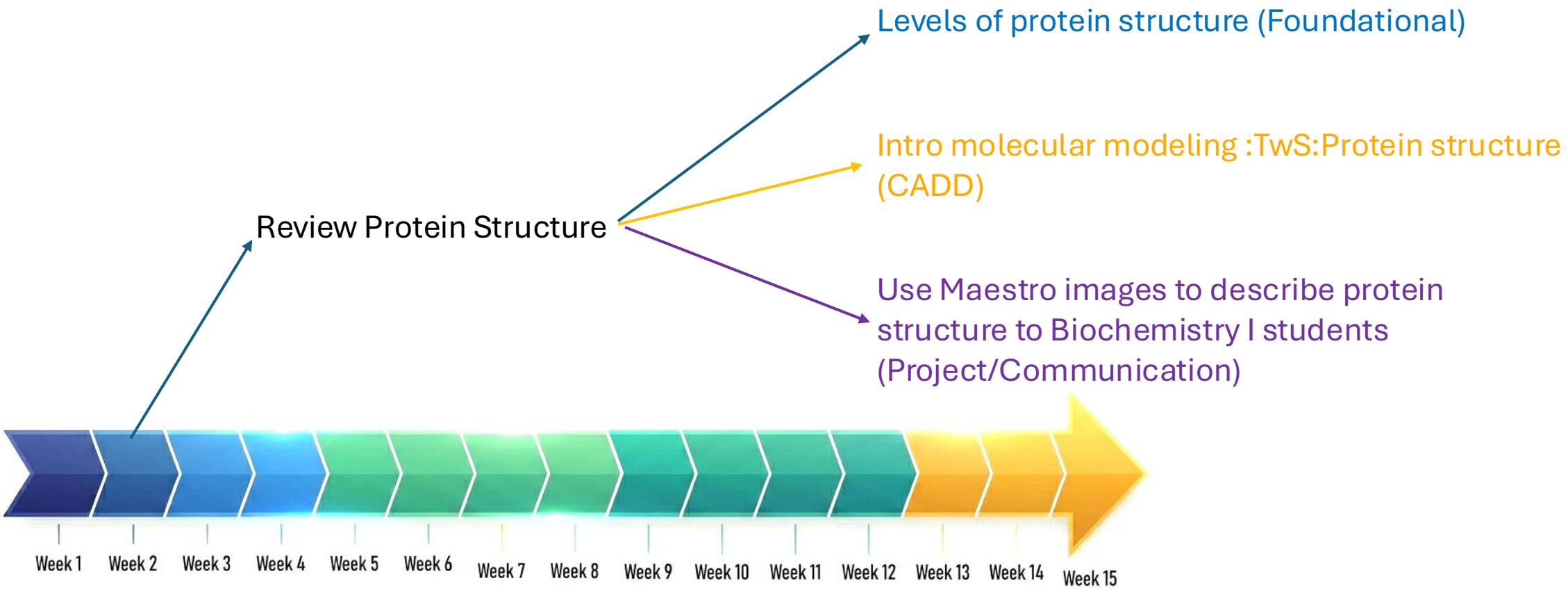


From student evaluations Fall 2025

“The activities and assessments were very helpful in understanding how to better use Maestro and on preparing for our final project.”

“I thought activities and reading assignments were really interesting. I loved everything about this class.”

Early topic scaffolding: protein structure



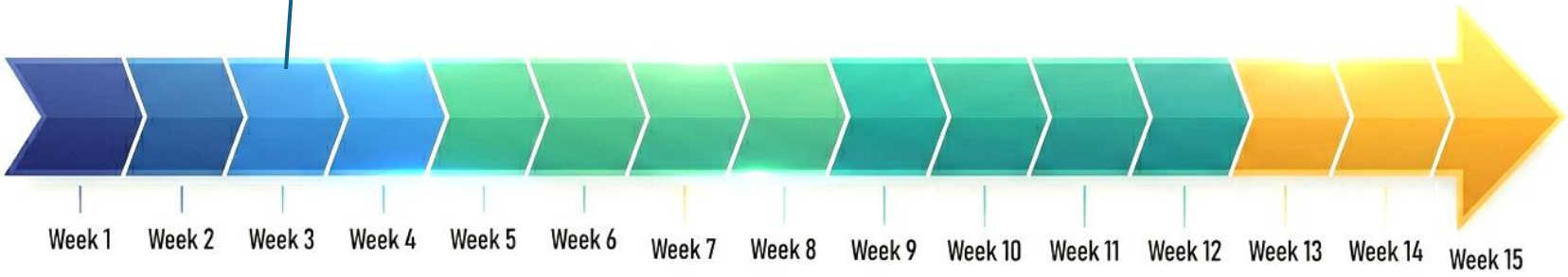
Early topic scaffolding: Intermolecular forces

Intermolecular Interactions

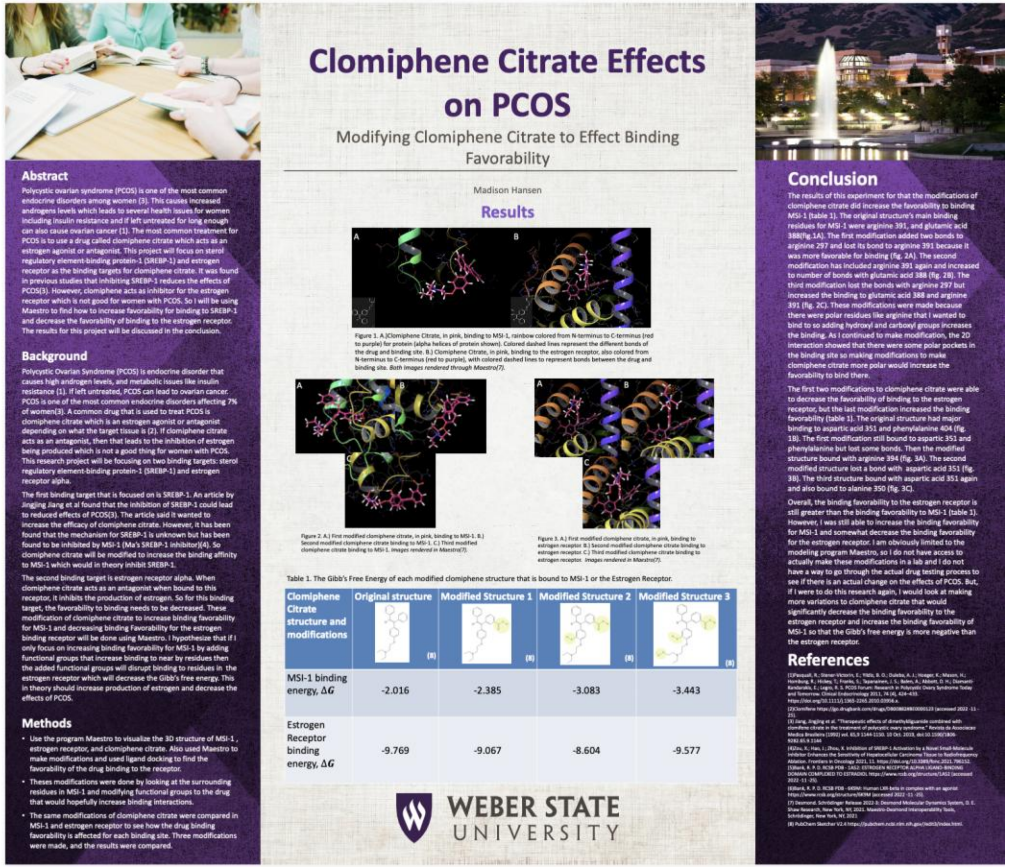
Types of IMFs (Foundational)

Example IMFs in protein/ligands from primary literature (Project/background)

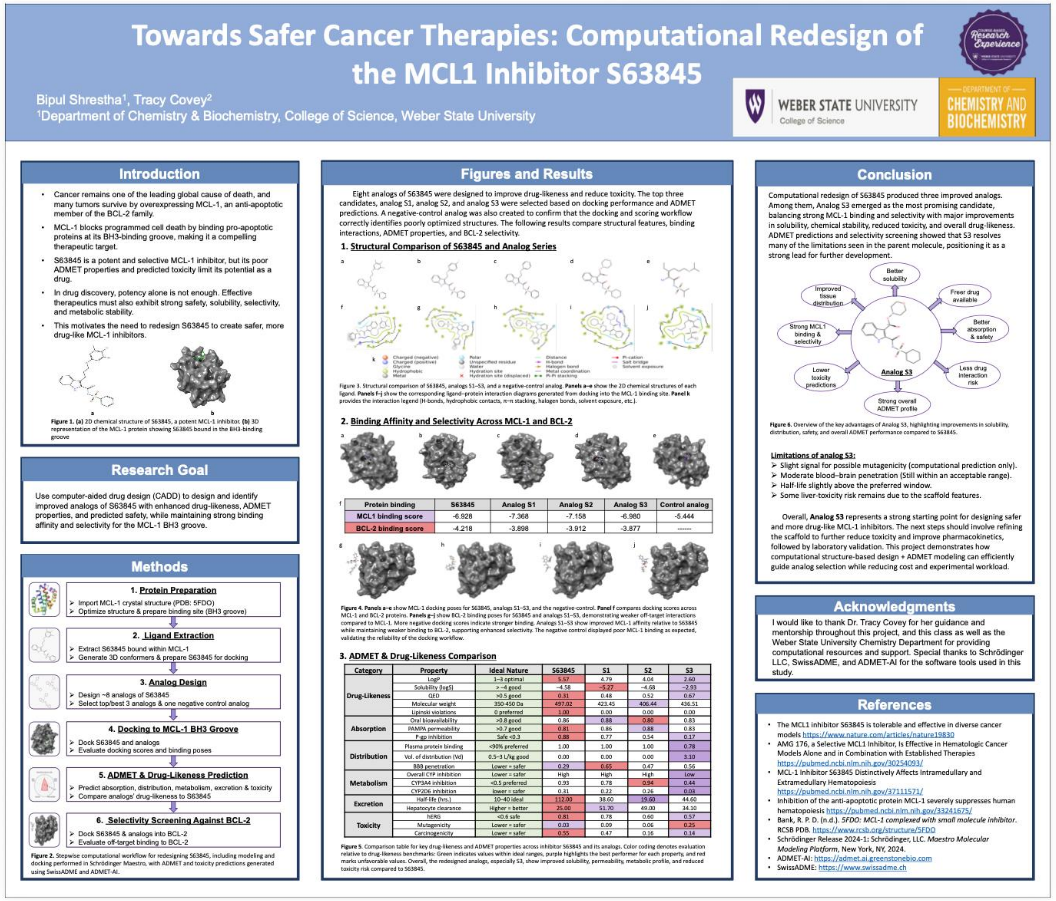
Use Maestro to “recreate” literature figures using interaction diagrams (CADD)



Medicinal Chemistry CURE:
Product example development



Fall 2021



Fall 2025

In summary:

- Accessibility: what your students can afford AND can use easily
- Technical literacy: involves learning and using the language and programs necessary for students' CURE project
- Timing: You can't start this too early!

Acknowledgements:

- Kat Bay, the Teaching with Schrodinger team
- Weber State's Office of Undergraduate research (funding)
- My Medicinal Chemistry students