A "Crowdsourcing" Team-Based Learning Approach to Teach Structure-Based Drug Design

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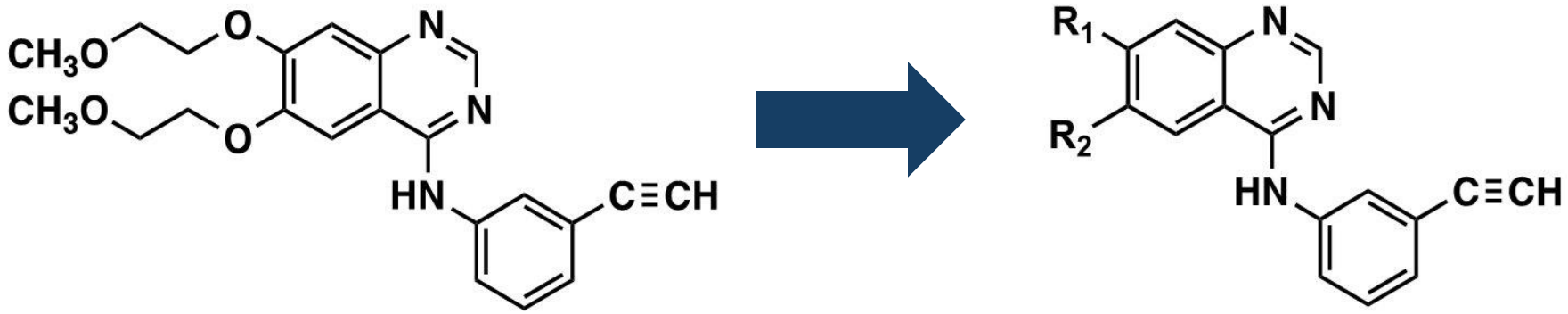
Principles of Drug Design Elective Course

PHRM 8213 offered at Fairleigh Dickinson University College of Pharmacy and Health Sciences (Florham Park, NJ)

3 credit, semester-long elective course offered to professional pharmacy students (PharmD) and graduate students (MS) in pharmacology

Uses **4 design challenges** for drug redesign; challenges are considered tasks that need to be completed by students (crowdsourcing model)

The Challenges



GOAL: Develop EGFR kinase inhibitors

Challenges/Tasks to complete the goal:

- Drug must retain common EGFR kinase inhibitor pharmacophore.
- **Challenge 1: Affinity** docking score for target EGFR kinase: ≤ -8 kcal/mol
- **Challenge 2:** Groups added must improve **solubility and maintain physiochemical properties**
- **Challenge 3:** Groups added must be predicted to have **metabolic stability**
- **Challenge 4:** Groups added must improve **affinity for resistant variant of EGFR (T790M)**
- Teams that win the most challenges are the drug design winners!

Design Challenge: Student Workflow

- **Resources needed:**
  - Slide deck or informational packet about common strategies for each challenge with cases or examples.
  - **Maestro/Small Molecule Basic Docking Package: Protein Prep, LigPrep, Glide (Instructor)**
  - **Maestro Free Academic Version (Students)**
  - **Databases**: Pubchem, Protein Data Bank (PDB)

- **Challenge Workflow:**
  - Students download free **Maestro** to import erlotinib template from Pubchem (SMILES or 3D Structure).
  - Students use Maestro 2D sketcher to make changes to compound, name and save files, and submit for each challenge.
  - Each group has a Directory/Folder (Google Drive or OneDrive) to upload compounds as a group for each challenge.
  - Students upload compounds by the deadline.
  - The instructor will assess compounds for each challenge.

Design Challenge: Instructor Workflow

Challenge 1: Affinity

Target: PDB 4HJO, Protein Prep; Receptor Grid Calculation; Dock control compound erlotinib

Compounds: Examine visually; LigPrep; Glide to calculate docking scores

Challenge 2: Physiochemical Properties

Calculate standard molecular properties

Check against both Lipinski's and Verber's Rules

Challenge 3: Metabolic Stability

CYP predictor or QikProp

Challenge 4: Affinity for T790M Variant

Target: PDB 2JIT, Protein Prep; Receptor Grid Calculation; Dock Control Compound

Compounds: Examine visually; LigPrep; Glide to calculate docking scores

Post-Challenge Faculty Debrief

Instructor compiles all results and sends to students; results include all structures for SAR analysis.

A summary of the best compounds for each week are presented to the class.

Instructor provides insights for best compounds and submissions for each challenge.

Properties	Erlotinib	Best Drug Candidate
Affinity Design		
Docking Score – Wild-type	**-8.252 kcal/mol**	
Docking Score – T790M Mutant	**-5.471 kcal/mol**	
Solubility Design		
Molecular Weight	393.44 g/mol	
# H Bond Donors	1	
# H Bond Acceptors	7	
LogP	2.7	
Polar Surface Area (PSA)	74.73 $Å^2$	
# Rotatable Bonds	10	
Metabolic Stability		
CYP3A4 % Metabolic Stability	51%	

Student Worksheets: *After each challenge, students complete an analysis for best and worst compound submission and compare properties with erlotinib.*

Post-Challenge Student Analysis & Reflection

Student Feedback & Personal Insights

Crowdsourced-competition format is perceived as a fun way to learn a complex topic; students take the challenges seriously.

Students gain an appreciation of the drug design process; designing a compound that meets all 4 challenges is difficult.

Students gain a better understanding of medicinal chemistry topics outside core course lectures (i.e. concept of SAR, pharmacophores becomes clearer).

Instructor can use any target/drug of interest with available structural data.

Resources

Schrödinger Small Molecule Drug Discovery Suite

Databases

- PubChem
- Protein Data Bank
- SMARTCyp

Targets & Compounds Used

- Erlotinib
- EGFR Kinase wild-type
- EGFR Kinase (T790M)

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