# Development of a Drug Discovery Simulation Laboratory Exercise in the Pharmaceutical Sciences Graduate Program Curriculum

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# Outline

- Overview of Curriculum (Worcester/Manchester)
  - Graduate Coursework / Laboratory Sequence
  - Laboratory Exercise Development
- Software & Data Selection
- Laboratory Workflow & Examples
  - Results / Issues
- Future Directions



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# PharmD Program Overview

- 300 Students / year
- DE Worcester / Manchester
- PharmD (Accelerated)
- Coursework in MedChem, Pharmacology & Toxicology
- Many w/ a Chemistry or Biochemistry B.S. Degree

➢ **Need for Electives**

➢ **Mobile Technology**


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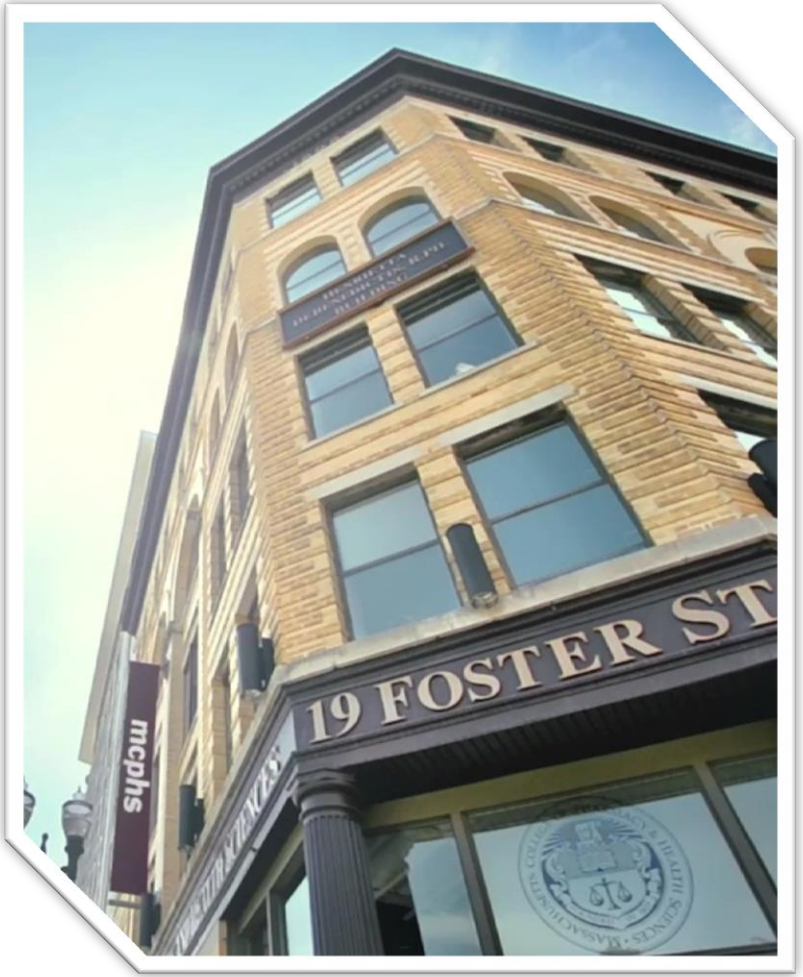
# Graduate Program Overview

- 2-4 Students / year
- Worcester
- Programs in Pharmacology or Pharmaceutics
- M.S. & Ph.D.

- Courses DE Boston
- Introduction to Pharmaceutical Sciences

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# Material Covered in Lecture

- ***"Introduction to Pharmaceutical Sciences" Lecture Course***
- ***Medicinal Chemistry Focused Topics:***

  - ❑ **Acid / Base Properties / Ionization State**
  - ❑ **Review of Organic Functional Groups**
  - ❑ **Water Solubility / LogP / LogD**
  - ❑ **Polar Surface Area (PSA)**
  - ❑ **Rule of 5**
  - ❑ **SAR (Sterics / Conformation / Electronics / Stereochemistry)**
  - ❑ **QSAR / 3D-QSAR**
  - ❑ **Bioisosteres / Scaffold Hopping**
  - ❑ **Principles of Drug Metabolism**
  - ❑ **ADME**



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# Laboratory Exercise Development

- **6 Lab Rotations (5 Weeks Each)**
  - **Follows the "Introduction to Pharmaceutical Science" Course**
  - **Covers basic lab techniques in Pharmacology & Pharmaceutics**
  - **Also designed to aid the student in choosing a Faculty Mentor**
  - ***1 Rotation in MedChem***

- **Problem: How to provide a meaningful MedChem lab experience during the rotation that would have application in a Pharmacology or Pharmaceutics program**

- **Decision: Introduce a simulated MedChem discovery program**



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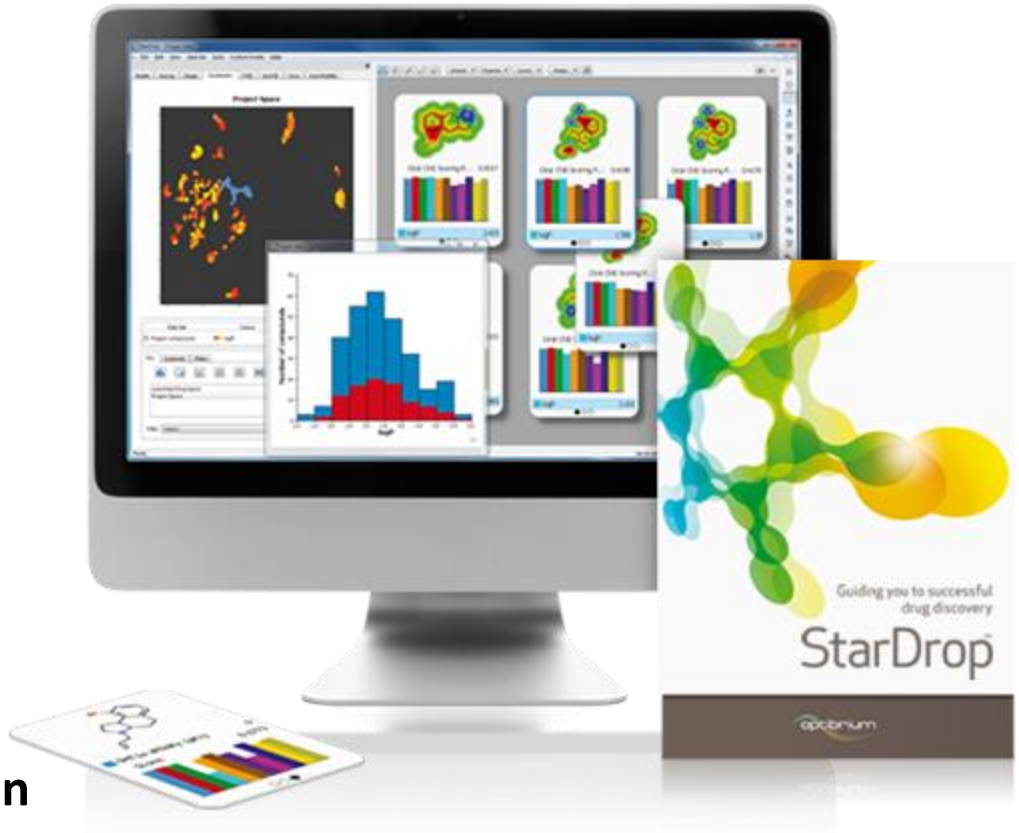
# Laboratory Exercise Development

1. **Software Selection**
   - **Optibrium StarDrop™**
   - **iPad Apps**




- **iPads not universally owned**
- **Apps available still in infancy**
- **Multiple Apps & Horsepower**
- **Familiarity w/ StarDrop™**
- **Glowing Molecule™**
- **Possibility of adding modules in the future if successful**

- **http://www.optibrium.com/stardrop/**



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# Laboratory Exercise Development

## 2. Screening Data Selection

- ChEMBL – NTD Database
- Malaria Screening Data

- Screening Results Available

- Already using literature example in lecture
  - *Nature* 465, pp. 305–310 (20 May 2010)

- https://www.ebi.ac.uk/chemblntd




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# Lab Exercise Development & Workflow

- Download Data
  - Scrub Data
    - Remove unneeded data columns
    - Remove metals, salts…
  - Fragment into smaller libraries
    - Faster processing of datasets
    - An attempt to prevent the same chemical series to be found by multiple students
    - Provide students with secondary screening library to search for like scaffolds to develop SAR
  - Libraries with approx. 1000 compounds each



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# Lab Exercise Development & Workflow

- Distribute Data
  - Demonstrate StarDrop™ Software
  - Explain Objective of Exercise
    - Perform primary screen
    - Identify 2 hit series based on:
      - Physicochemical Properties
      - Activity

- 1st Exercise
  - Students receive fragmented datasets
  - Students run calculations and choose 2 hit series



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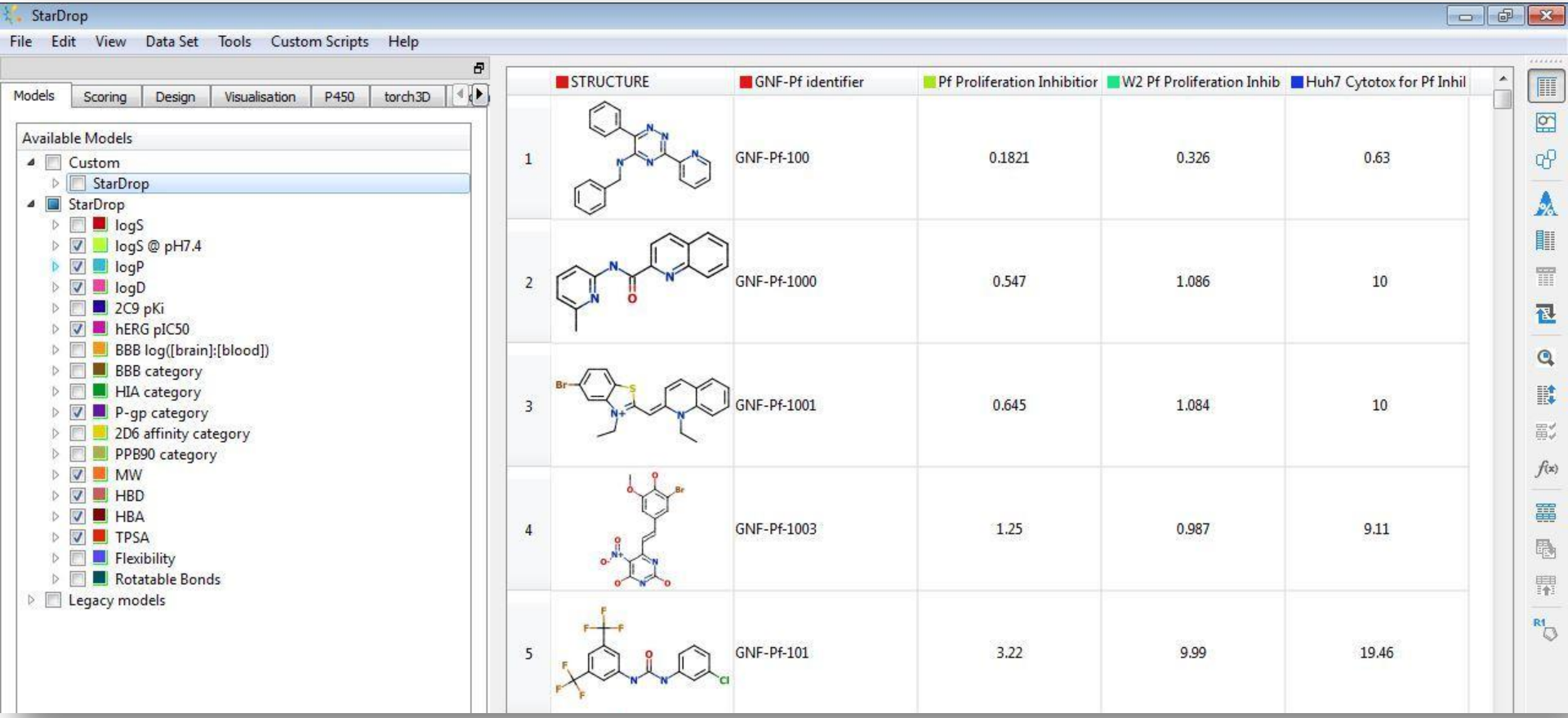
# Initial Student Calculations & Data Triage

- Students Run Selected Calculations



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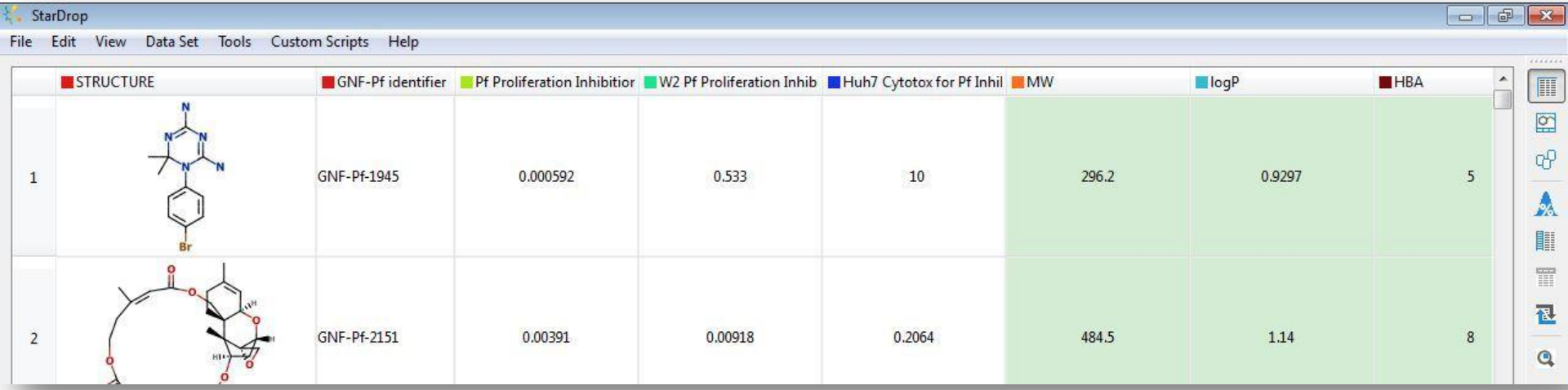
# Initial Screening Hits by Students

- General Trends in Results from the 1st Exercise
  - Students tended to focus choices on Activity
    - ➢Generally observed Ro5
    - ➢Little concept of scaffold searching and SAR
    - ➢Little use of Visualization vs. Spreadsheet View




| | STRUCTURE | GNF-Pf identifier | Pf Proliferation Inhibitior | W2 Pf Proliferation Inhib | Huh7 Cytotox for Pf Inhil | MW | logP | HBA |
|---|---|---|---|---|---|---|---|---|
| 1 |  | GNF-Pf-1945 | 0.000592 | 0.533 | 10 | 296.2 | 0.9297 | 5 |
| 2 |  | GNF-Pf-2151 | 0.00391 | 0.00918 | 0.2064 | 484.5 | 1.14 | 8 |



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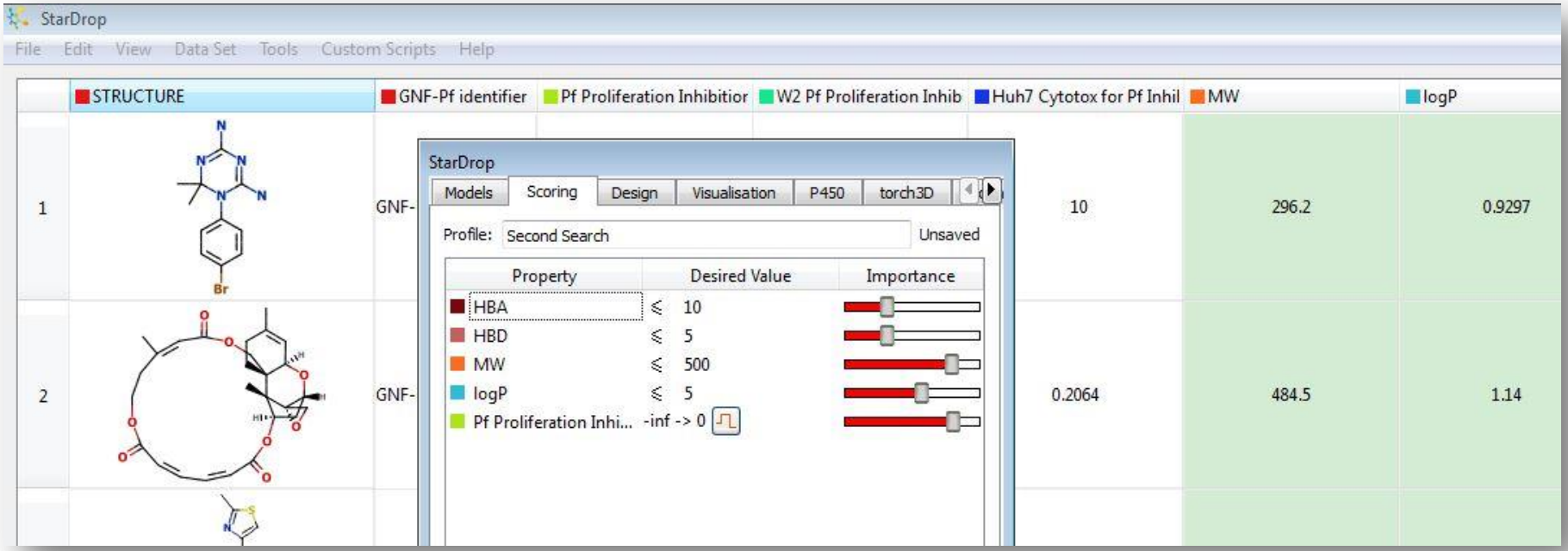
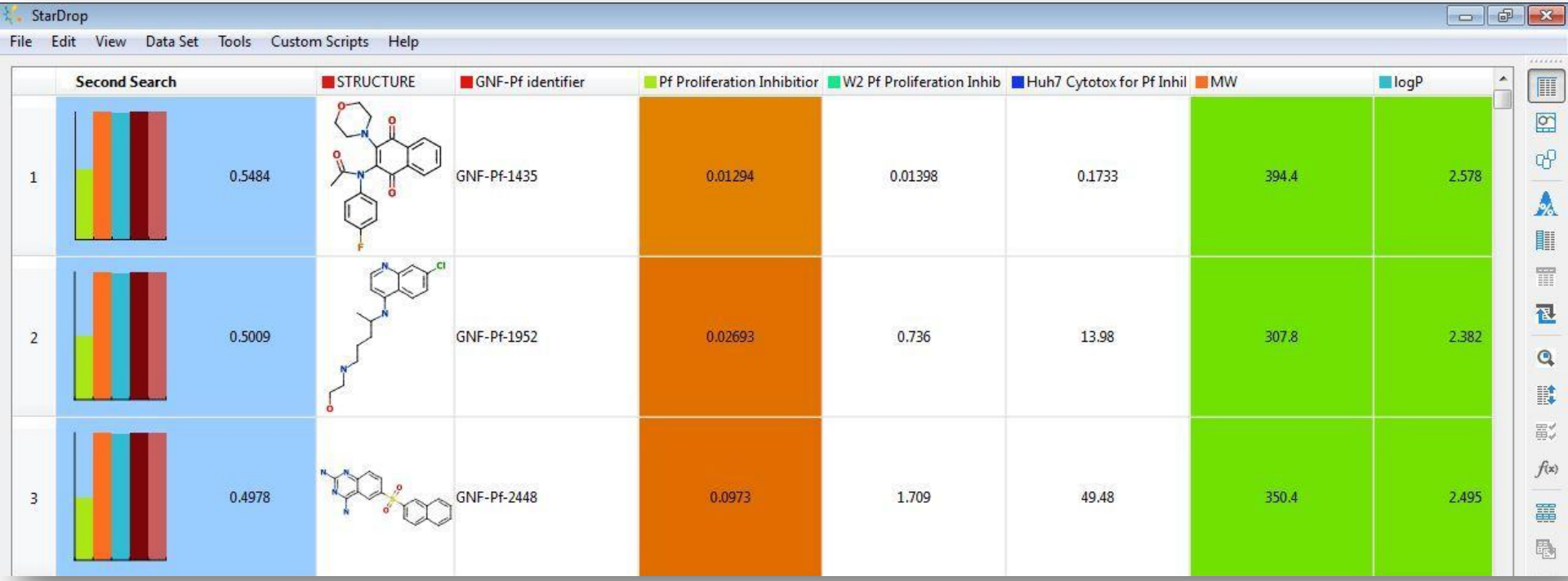
# Follow-on Screening Triage

- 2nd Exercise – Utilize Scoring Function
  - Students are made to consider all physicochemical parameters in addition to activity – *Composite Score*
  - Students Again Asked to Choose Top 2 Hits
    - Based partially on SAR from structure searches



# Follow-on Screening Triage

- General Trends in Results from the 2nd Exercise
  - Overall, the students tended to find different hit compounds as compared to their first search
  - New appreciation of looking at additional information beyond activity




| | Second Search | STRUCTURE | GNF-Pf identifier | Pf Proliferation Inhibitior | W2 Pf Proliferation Inhib | Huh7 Cytotox for Pf Inhil | MW | logP |
|---|---|---|---|---|---|---|---|---|
| 1 | 0.5484 | | GNF-Pf-1435 | 0.01294 | 0.01398 | 0.1733 | 394.4 | 2.578 |
| 2 | 0.5009 | | GNF-Pf-1952 | 0.02693 | 0.736 | 13.98 | 307.8 | 2.382 |
| 3 | 0.4978 | | GNF-Pf-2448 | 0.0973 | 1.709 | 49.48 | 350.4 | 2.495 |

# Transition to Compound Optimization

- Transition to 3rd Exercise
  - Students informed that only enough resources are available to work on a single Series
    - Student then must begin to suggest modifications to potentially fix most serious compound liabilities
  - Evaluation of choice involves discussion of all characteristics of the chosen series
    - Activity / Selectivity
    - SAR (usually 3-10 analogs)
    - Calculated physicochemical parameters



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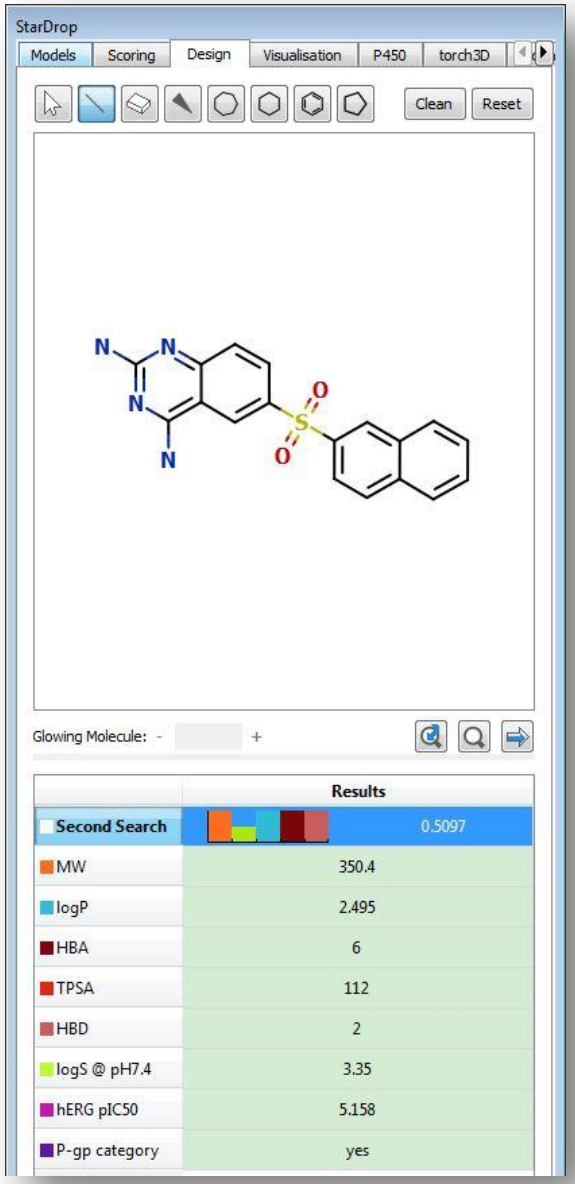
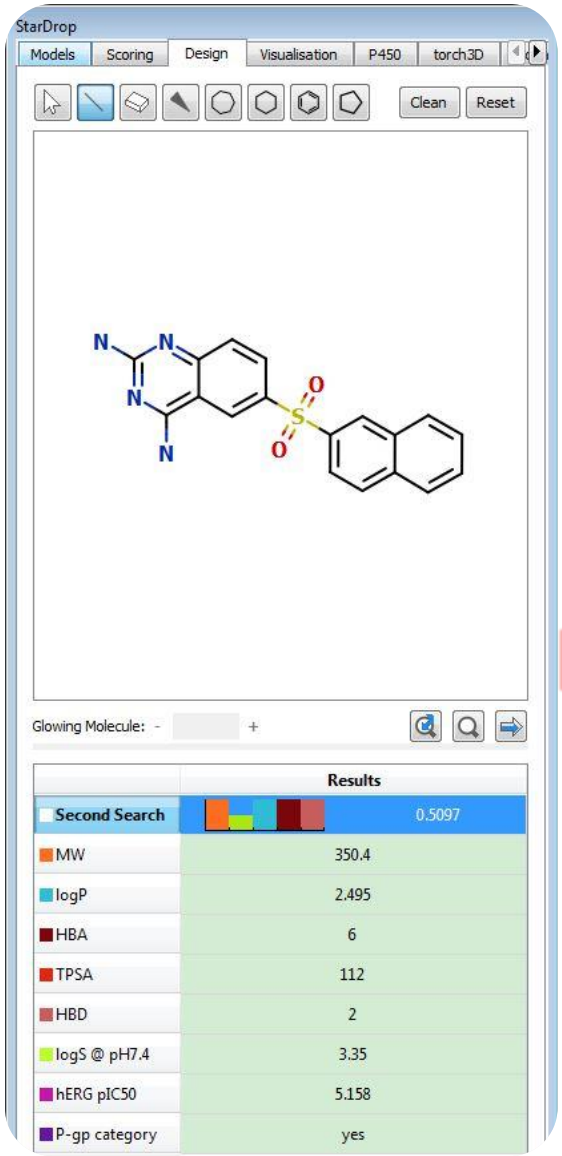
# Transition to Compound Optimization

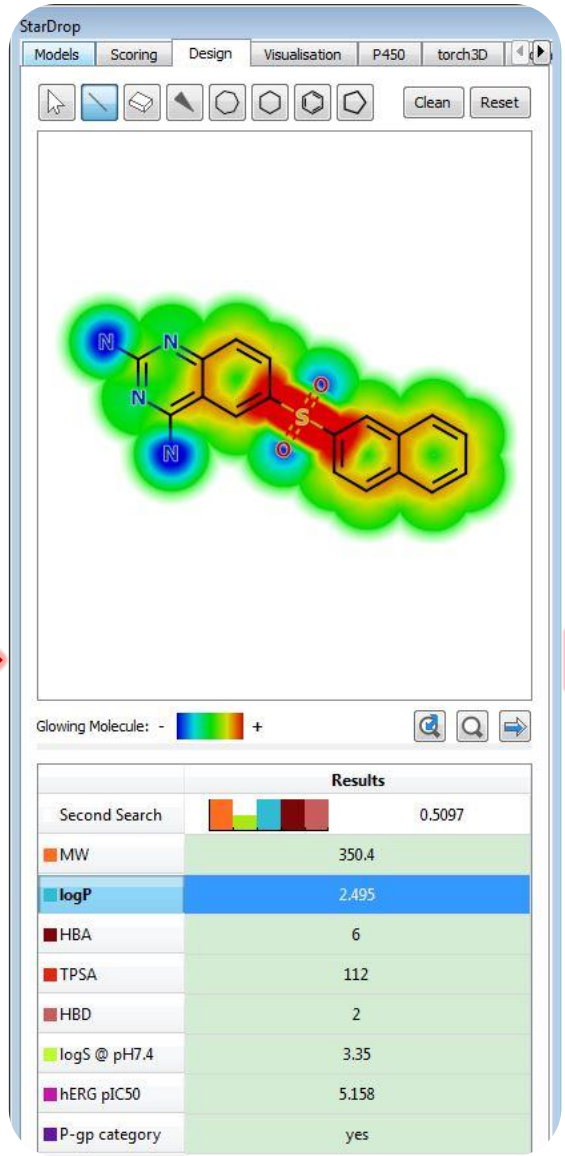


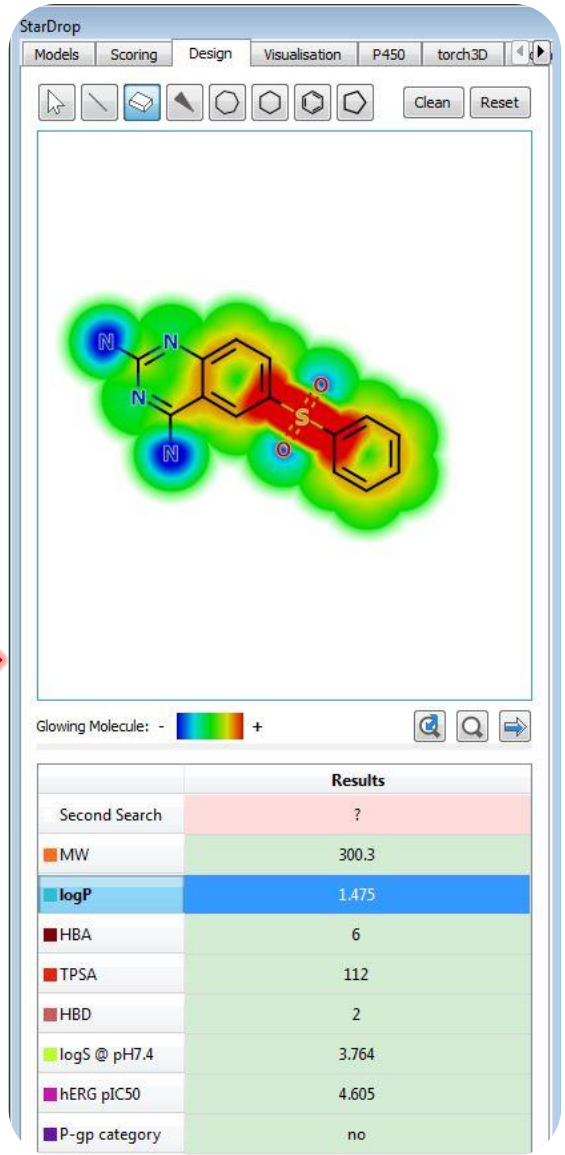

- Student Selected Single Hit Series
  - 3rd Exercise very open ended
  - Wide latitude given
  - Informed that any changes need to fit within available SAR if possible

  - *Most trying portion of lab exercise*
  - *Weakness in chemistry background difficult to overcome*
  - *Great deal of coaching required*
  - *Glowing Molecule™*

# Transition to Compound Optimization



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# Evaluation of Proposed Compounds

- Wrap-Up Exercises
  - Use of hit series and newly proposed analogs
  - Method to benchmark new analogs and illustrate that they are still very early on the discovery timeline
  - Provides a means to review Metabolism

    - **SMARTCyp Web Service**
    - **SAR Table© Model Building**



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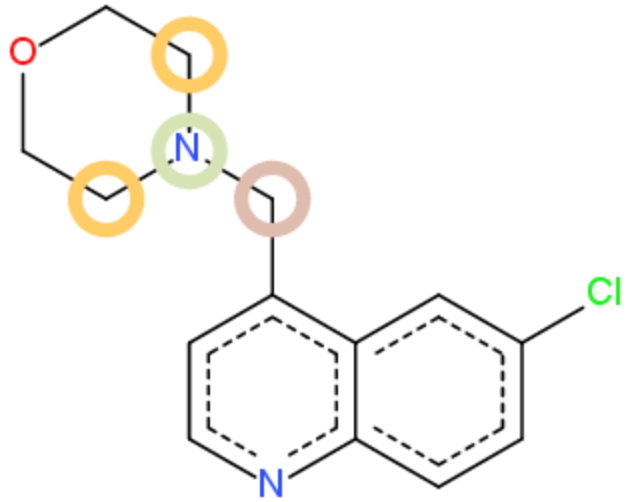
# Evaluation of Proposed Compounds

- SMARTCyp Web Service
  - Molecular series uploaded to server
  - Analogs judged in comparison to original compounds
  - "**Gamification**" of Results




Standard | CYP2C | CYP2D6

**1: null**

| Rank | Atom | Score | Energy | Accessibility | 2DSASA |
|---|---|---|---|---|---|
| **1** | **C.12** | **33.55** | **41.1** | **0.78** | **33.17** |
| **2** | **C.10** | **35.87** | **41.1** | **0.56** | **19.57** |
| **3** | **N.11** | **37.12** | **42.6** | **0.67** | **3.75** |
| 4 | C.13 | 53.59 | 62.2 | 0.89 | 37.53 |
| 5 | N.6 | 67.67 | 75.6 | 0.89 | 20.4 |
| 6 | C.4 | 68.99 | 77.2 | 0.89 | 27.38 |
| 7 | C.3 | 71.67 | 80.8 | 1 | 28.22 |
| 8 | C.18 | 73.71 | 80.8 | 0.78 | 21.6 |
| 9 | C.8 | 79.91 | 86.3 | 0.67 | 26.32 |
| 10 | C.7 | 84.45 | 92.0 | 0.78 | 33.21 |
| 11 | C.2 | 991.68 | 999 | 0.89 | 5.28 |
| 12 | C.5 | 992.49 | 999 | 0.78 | 7.23 |
| 13 | C.17 | 993.47 | 999 | 0.67 | 4.99 |
| 14 | C.9 | 994.46 | 999 | 0.56 | 2.37 |

P. Rydberg, D. E. Gloriam, J. Zaretzki, C. Breneman and L. Olsen, *ACS Med. Chem. Lett*., **2010**, *1*, 96-100; P. Rydberg, D. E. Gloriam and L. Olsen, *Bioinformatics*, **2010**, *26*, 2988-2989; P. Rydberg and L. Olsen, *ACS Med. Chem. Lett*., **2012**, *3*, 69-73; P. Rydberg and L. Olsen, *ChemMedChem*, **2012**, *7*, 1202-1209; P. Rydberg et al., *Angew. Chem, Int. Ed.,* **2013**, *52*, 993-997; and P. Rydberg et al., *Mol. Pharmaceutics*, **2013**, *10*, 1216-1223.



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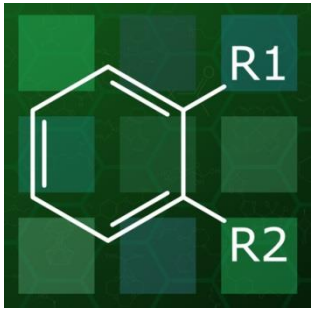
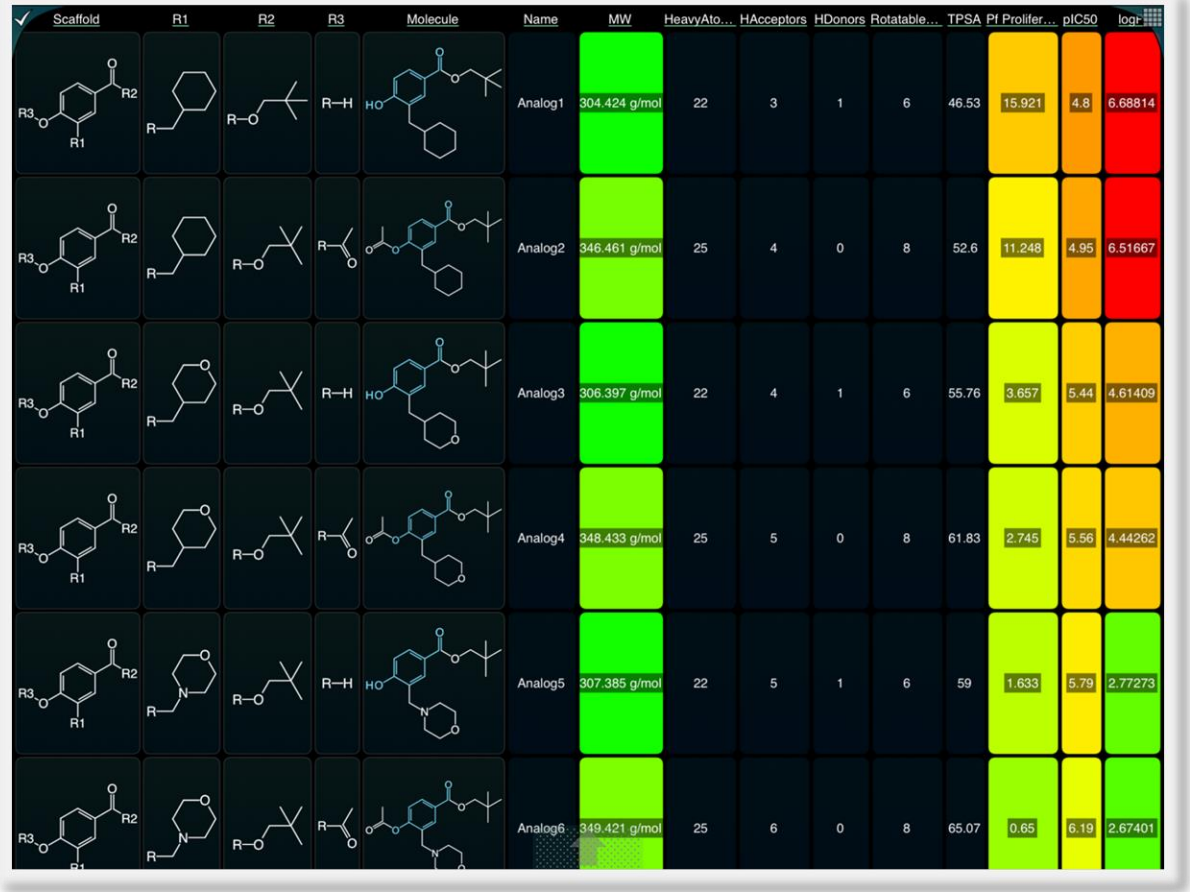
# Evaluation of Proposed Compounds

- SAR Table
  - iPad Application / Cheminformatics Tools
  - Ability to generate Schemes & Models




Used to generate predicted biological activity of new analogs.

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http://molmatinf.com/

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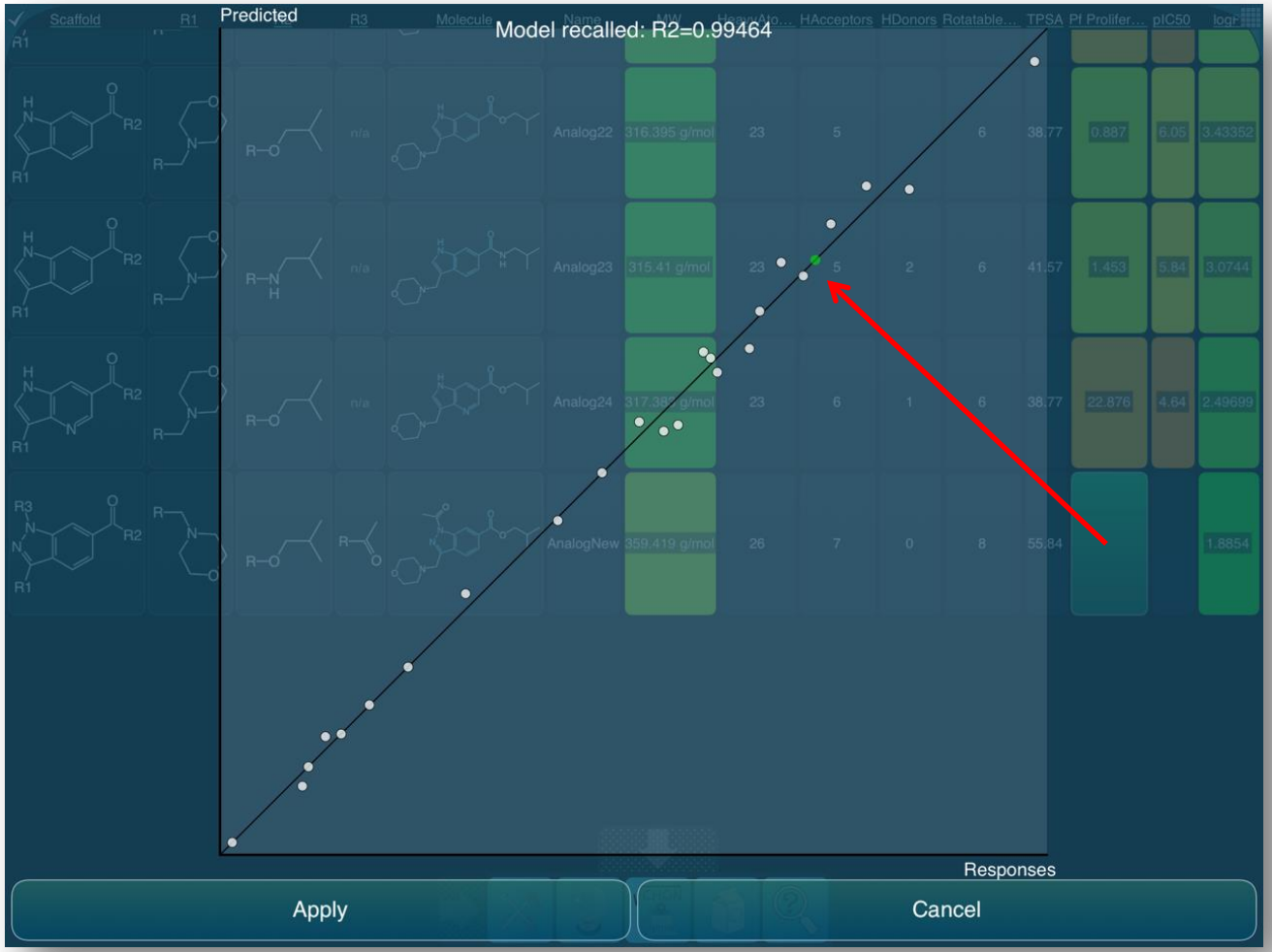
# Evaluation of Proposed Compounds

- SAR Table




1. Build a scheme for any of the properties calculated or experimentally derived.
2. Application builds model and makes prediction.



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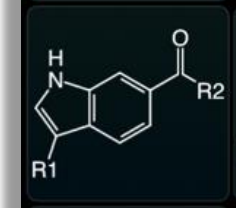
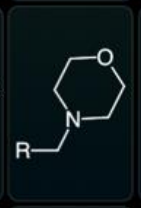
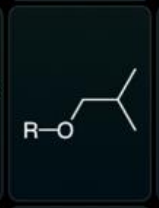
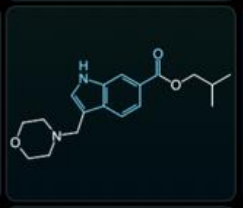
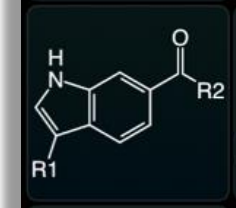
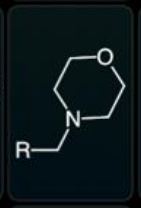
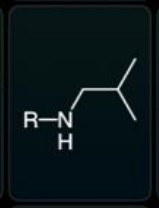
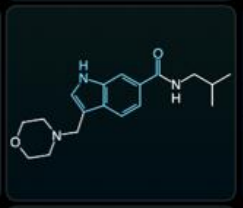
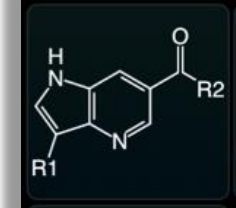
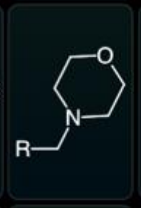
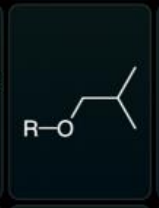
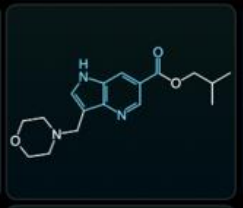
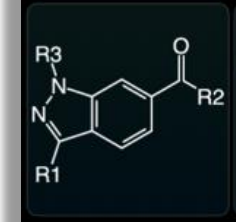
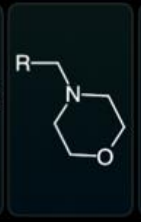
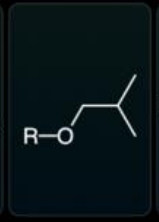
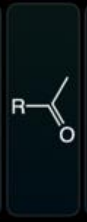
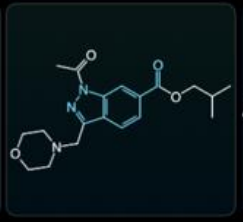
# Evaluation of Proposed Compounds

- SAR Table

| Scaffold | R1 | R2 | R3 | Molecule | Name | MW | HeavyAto… | HAcceptors | HDonors | Rotatable… | TPSA | Pf Prolifer… | pIC50 | logP |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
|  |  |  | n/a |  | Analog22 | 316.395 g/mol | 23 | 5 | | 6 | 38.77 | 0.887 | 6.05 | 3.43352 |
|  |  |  | n/a |  | Analog23 | 315.41 g/mol | 23 | 5 | 2 | 6 | 41.57 | 1.453 | 5.84 | 3.0744 |
|  |  |  | n/a |  | Analog24 | 317.383 g/mol | 23 | 6 | 1 | 6 | 38.77 | 22.876 | 4.64 | 2.49699 |
|  |  |  |  |  | AnalogNew | 359.419 g/mol | 26 | 7 | 0 | 8 | 55.84 | (0.774581 µM) | (5.846 96) | 1.8854 |



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# Current Status of Lab Exercise

- Lessons Learned
  - Positive response from students
  - Fills a gap in graduate curriculum
  - Effective method to review and reinforce abstract physicochemical properties covered in lecture
  - Identity of the Screening Target not important
  - Need to allow an iterative approach to any products (calculation runs, target selections, etc.) turned in by the students
  - ***Baseline chemistry knowledge weak and will not be correctable in the timeframes allotted***



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# Future Plans

- Scale and Expand Scope of Laboratory Exercise
  - Recycle current concept into Elective Course format
    - Pharm.D. Students
    - Scale to ~10 – 25 Students (*Need more data sets*)
    - Seed Screening Databases w/ Active Compounds (?)
  - Require additional simulated drug discovery tasks
    - Increase drug optimization cycles and requirements
    - hERG Pharmacophore Matching
    - Expand Metabolism Profiling / CYP Profile
    - Include Molecular Modeling / Docking
- Incorporate mobile software & platforms



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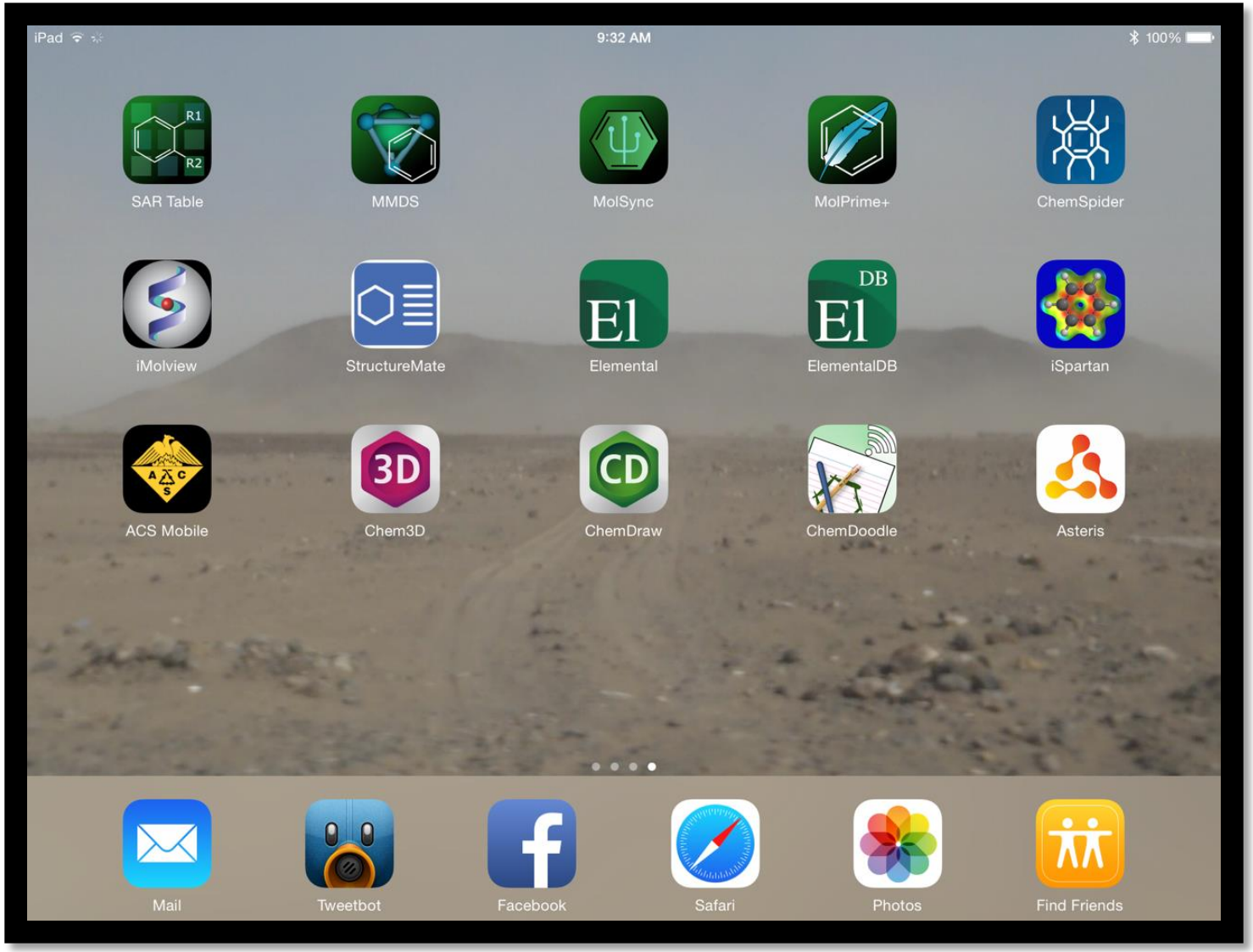
# Next Steps



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