Connecting small-molecule structure to biological activity

Predictive models of small-molecule transcription factor binding

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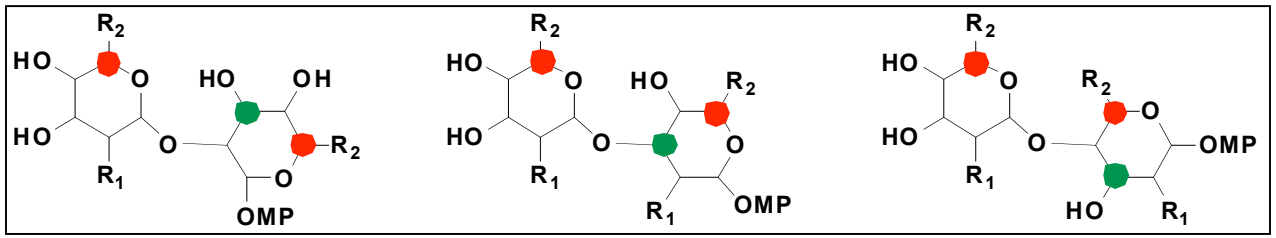
Why find structure activity relationship (SAR)?

- Drug and probe development
  - Efficient enhancement through structure optimization

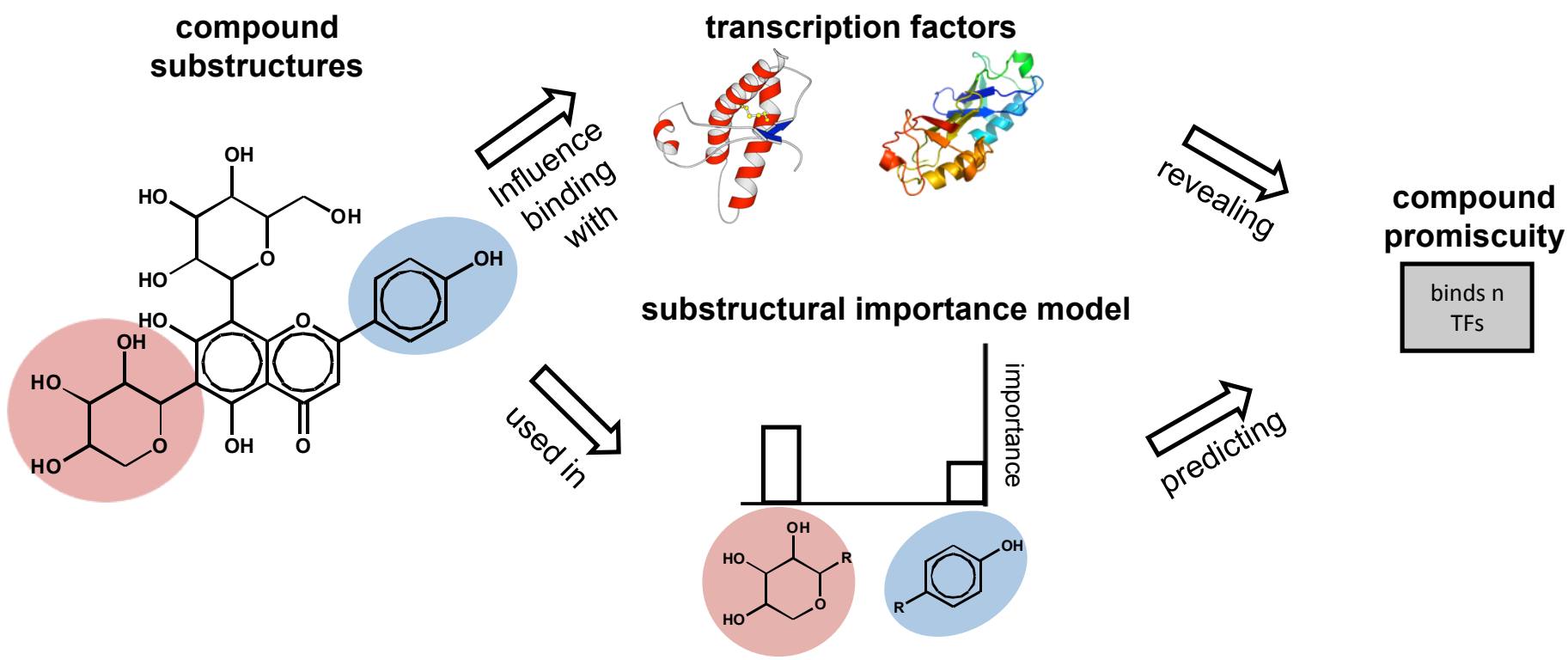
How is SAR currently found?

- Visual inspection of compound structures
- Limited computational techniques
  - One biological target, or
  - Constrained library diversity



Tanikawa et al. (2009) *J. Am. Chem. Soc.* **131:** 5575-5083

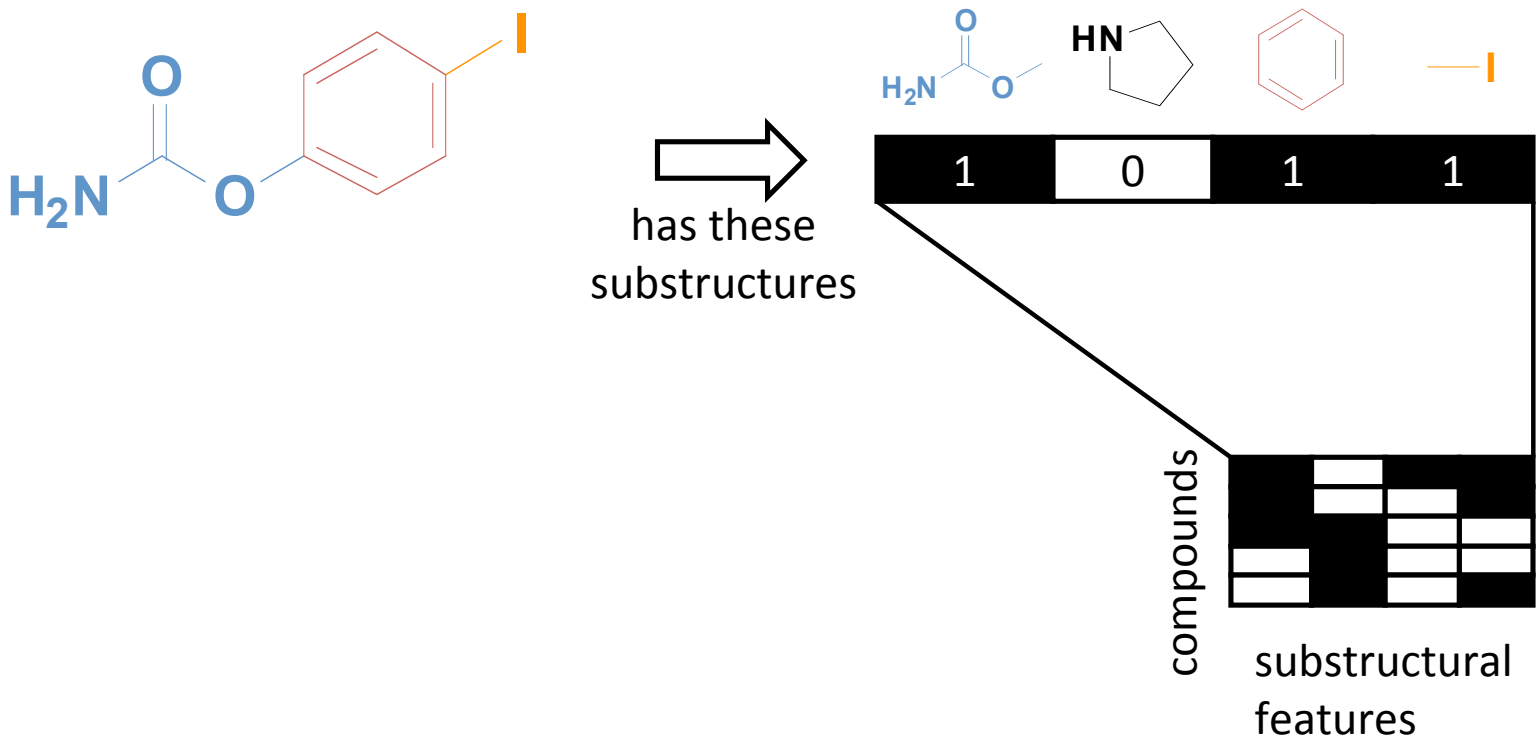
What is our new approach for finding SAR?



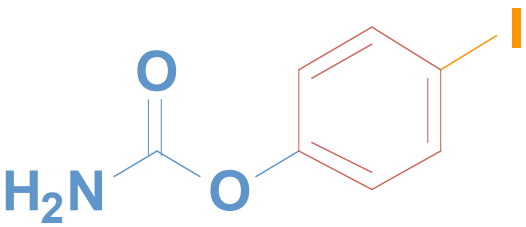
How do we find SAR?

1. **Describe structure and activity**
2. Create substructure-based predictive model
3. Interpret results

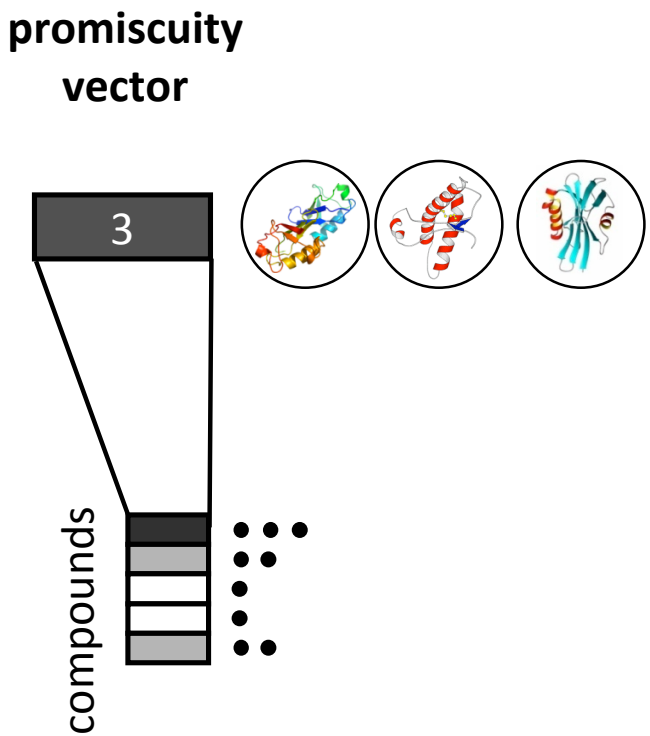
How do we represent structure?



How do we represent activity?



binds with



How do we find SAR?

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2. **Create substructure-based predictive model**
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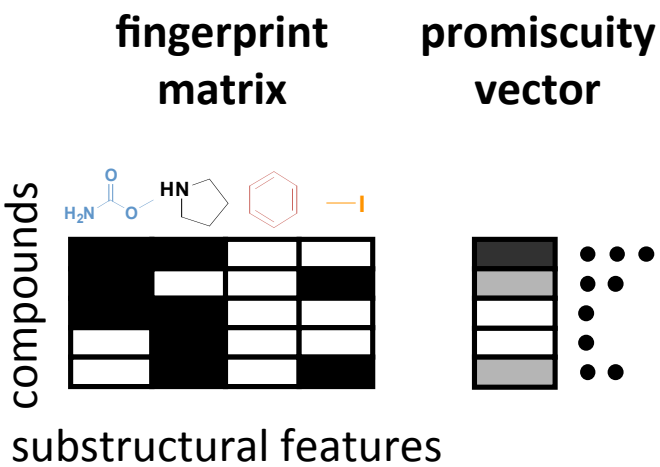
How does our model work?



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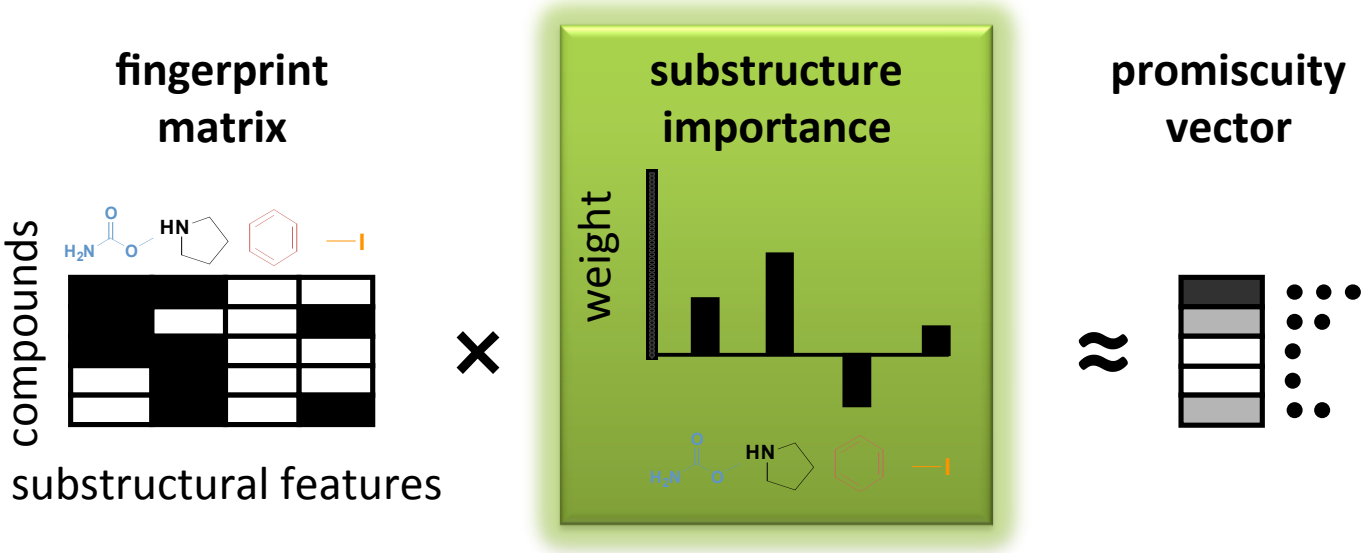
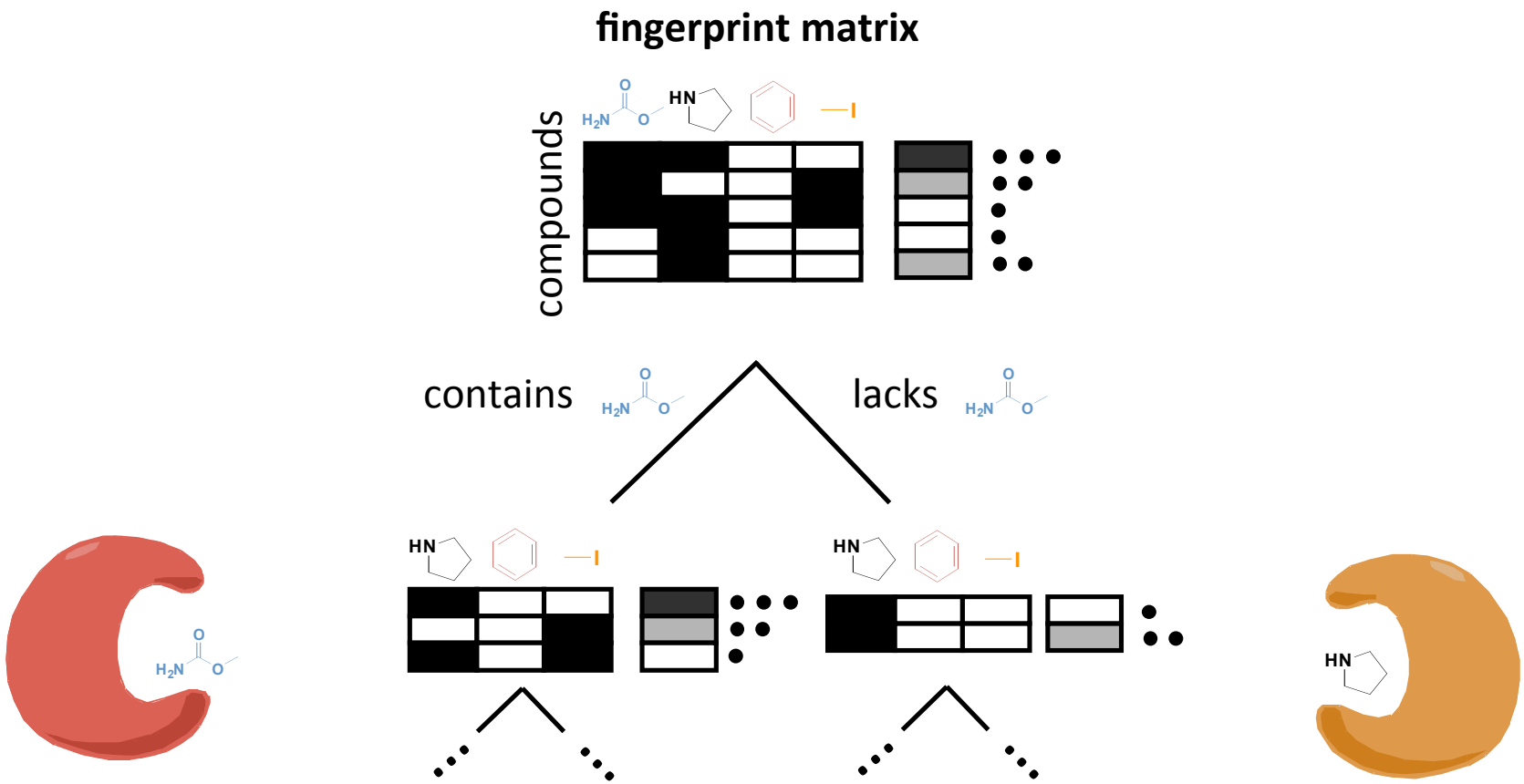


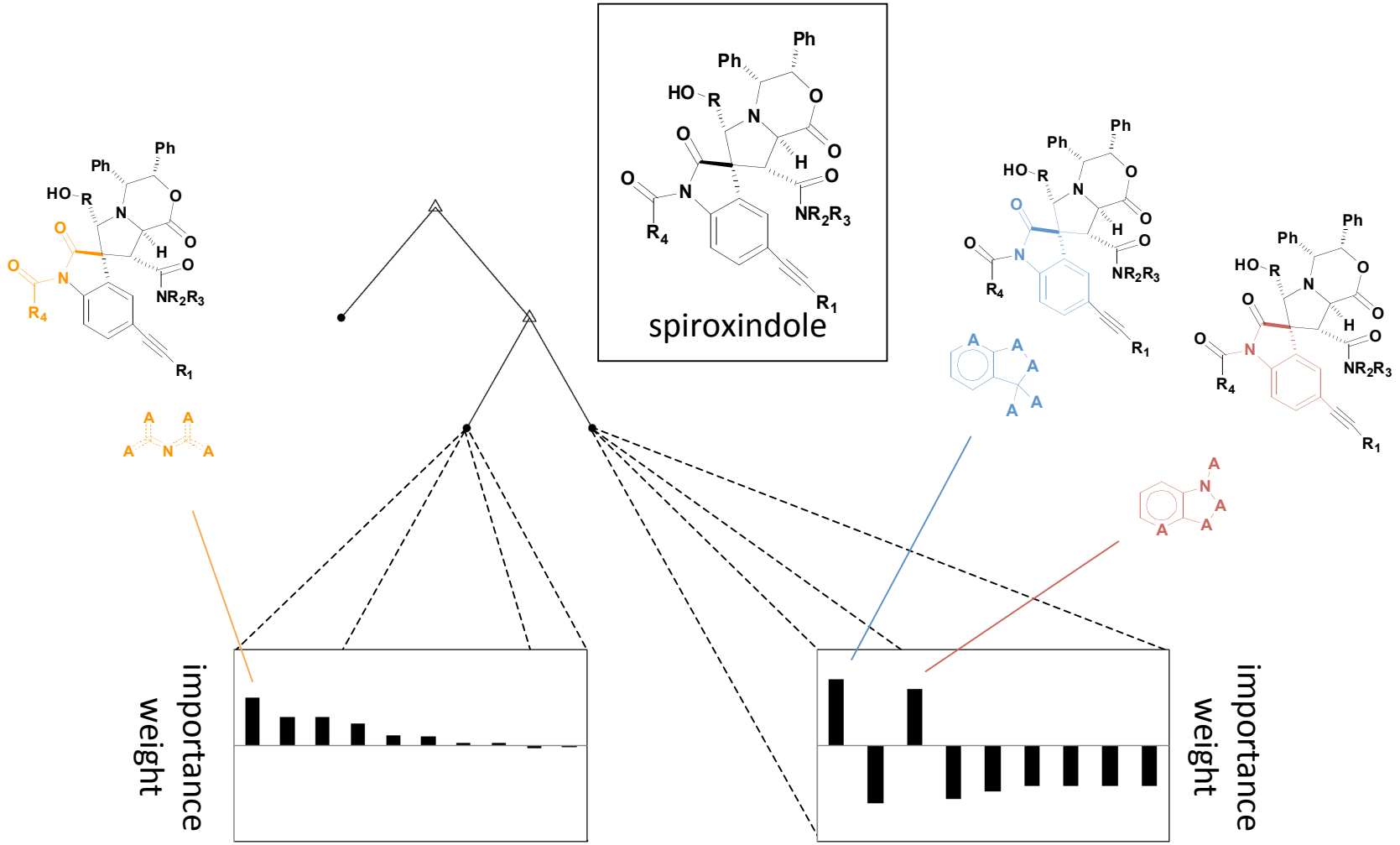
How do we handle different interactions?



How do we find SAR?

1. Describe structure and activity
2. Create structure-based predictive model
3. **Interpret results**

What substructures influence promiscuity in certain cases?



How do we find SAR?

1. Describe structure and activity
2. Create structure-based predictive model
3. Interpret results

What will we do in the future?

- Further investigate chosen substructures
- Different representations of promiscuity
- Generate larger substructures
- Additional sets of compounds

Acknowledgements

Analysis

Paul A. Clemons (mentor)
Joshua C. Gilbert
Hyman A. Carrinksi
Sandrine Muller
Nicole E. Bodycombe
Adam A. Margolin

Chemistry

Angela N. Koehler

Administration

Eboney Smith
Bruce Birren

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How do we find SAR?

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