A Tiered Screen Protocol for the Discovery of Structurally Diverse HIV Integrase Inhibitors

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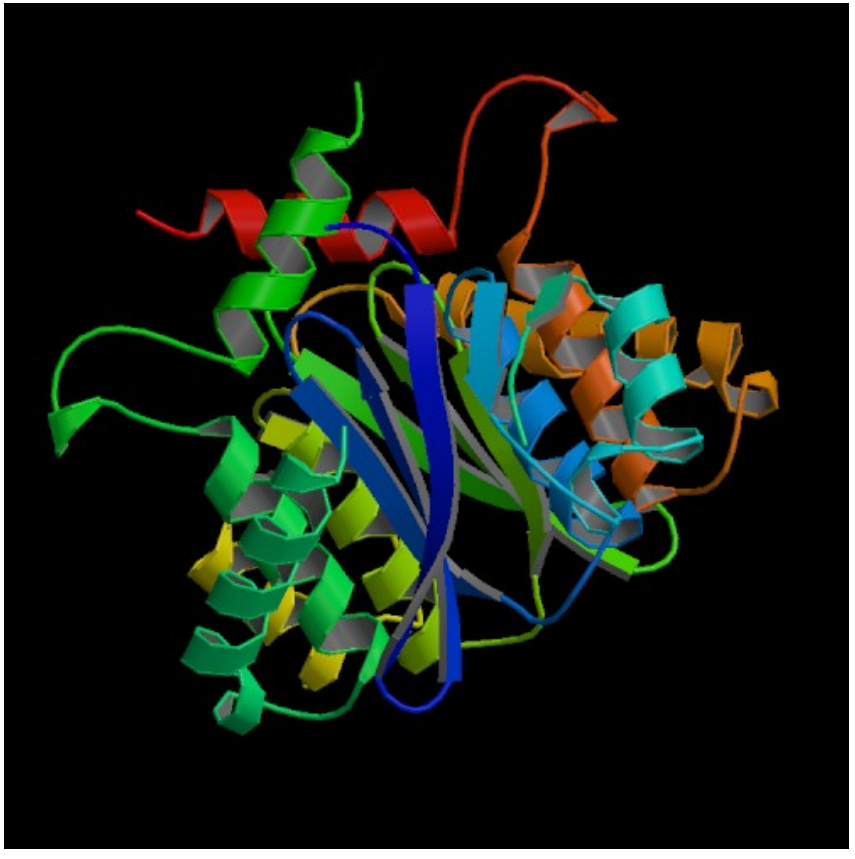
Background

- Most drugs target HIV reverse transcriptase or protease
- HIV integrase is vital for viral replication
- No drugs have been approved for HIV integrase



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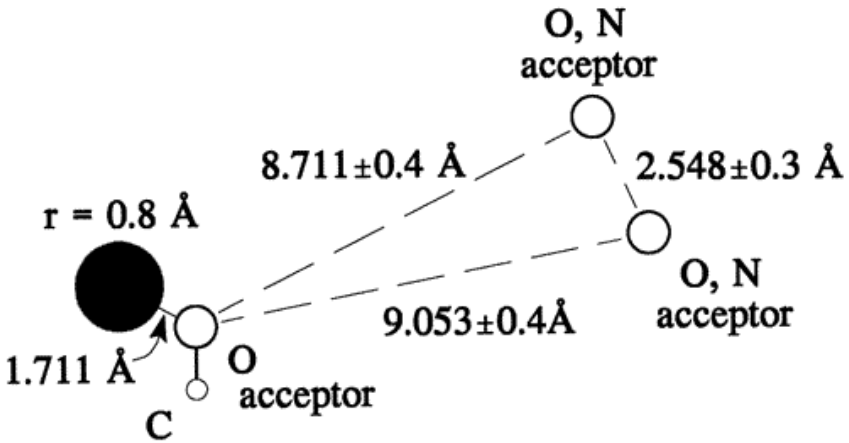
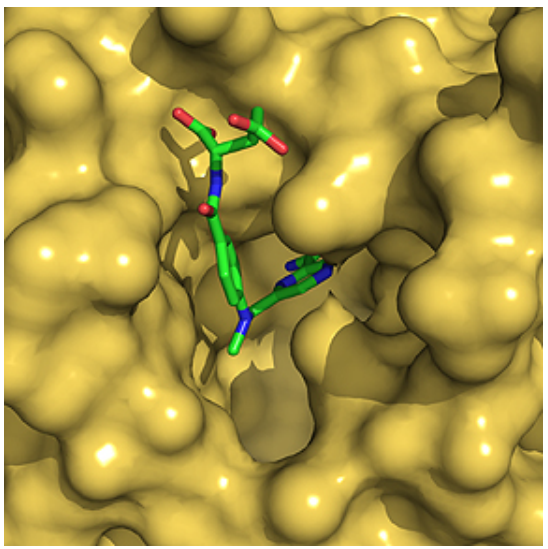
Previous Approaches

- Pharmacophores
- Docking
- Disadvantages
  - Requires a reliable receptor structure
  - Computationally intensive
  - Not necessarily diverse





Nicklaus, M.C. et al., *J. Med. Chem.*, **1997**, *40*, 920–929

Nair, V; Chi, G.; Neamati, N.; *J. Med. Chem.*, **2006**, *49*, 445–447

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Goals

- High speed
  - Be able to process large libraries rapidly
  - Avoid docking till required
  - Try and use connectivity information only
- Reliability
  - Use consensus approaches for prediction
  - Use molecular similarity
- Novely
  - Try to obtain a diverse set of hits
  - Try to obtain hits suitable for lead hopping

Datasets & Tools

Training Data

- Curated dataset
- 529 actives
- 395 inactives

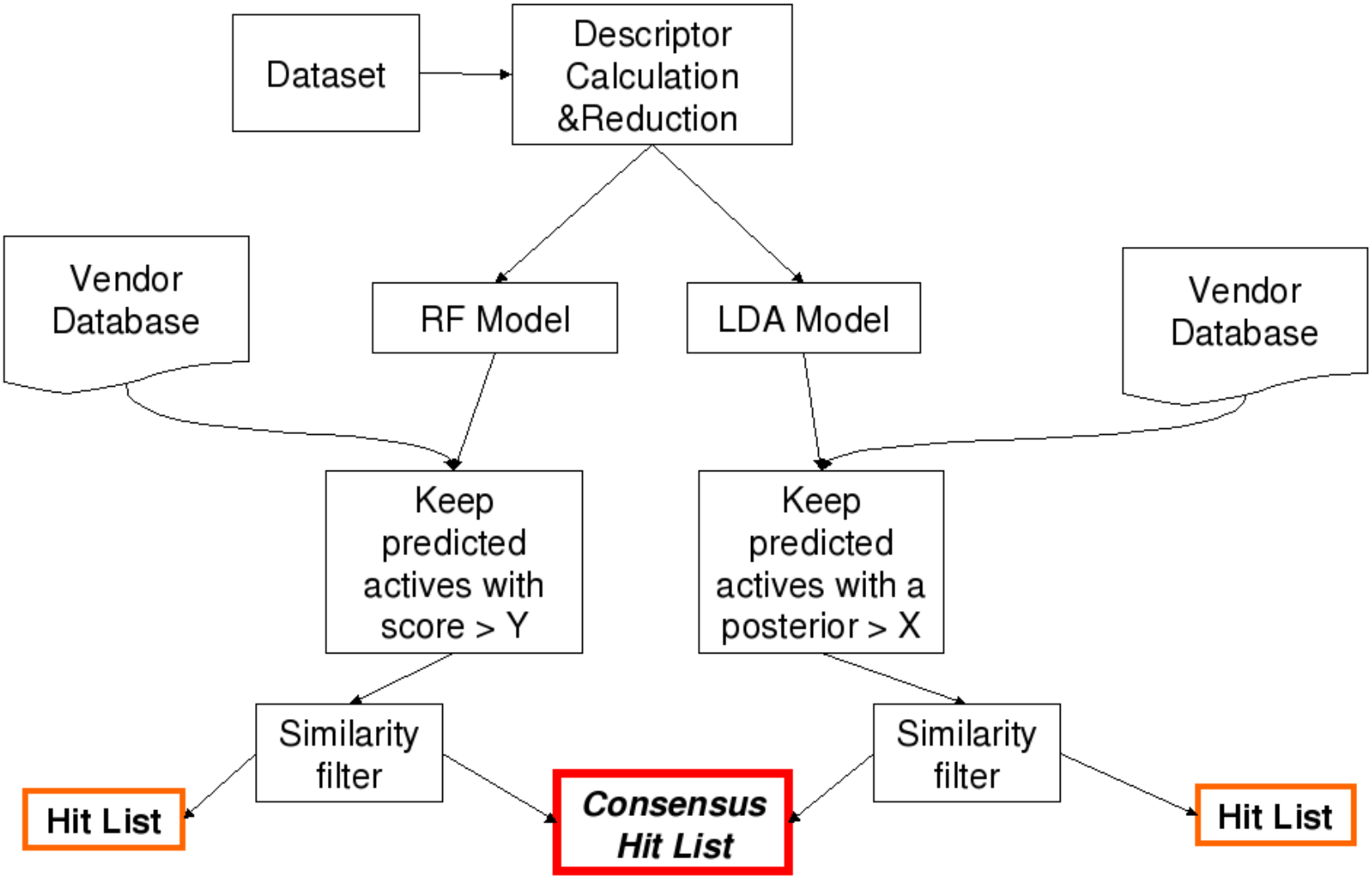
Vendor Database

- 50,000 compounds
- 2D structures

Software

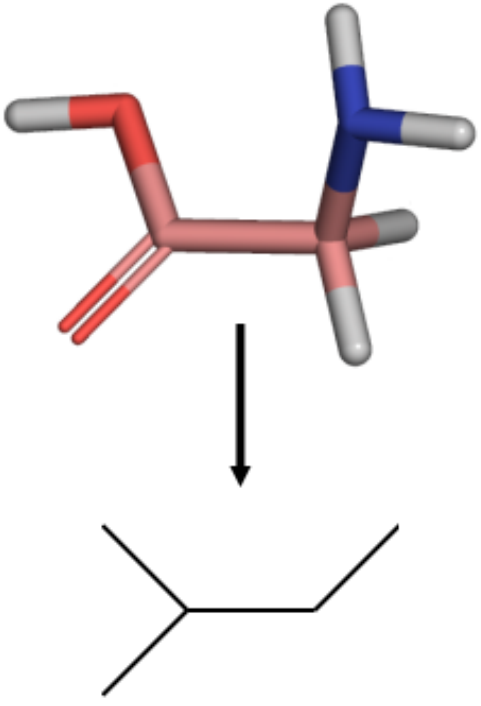
- MOE
- R 2.2.0
- `MASS`, `randomForest`, `fingerprint`

Overview of the Screening Protocol



Descriptor Calculations

- Restricted to topological descriptors
- Calculated 142 descriptors
- Removed low variance and correlated descrirptors
- Size of reduced pool was 45



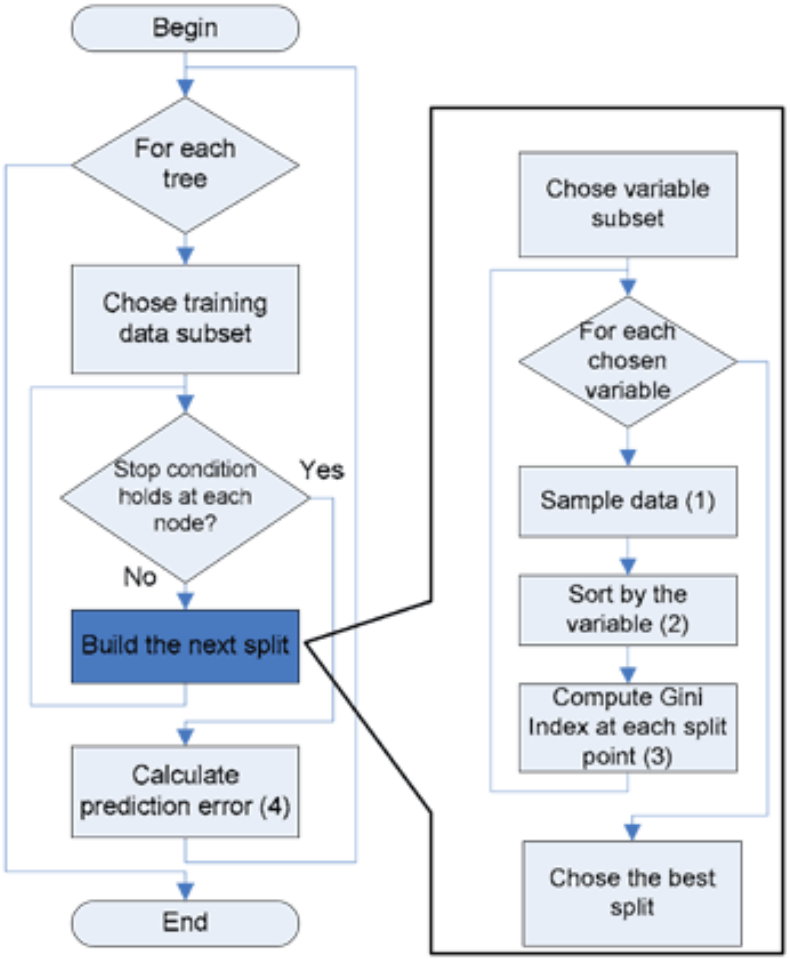
- Only considers 2D connectivity
- Very fast to compute

Predictive Models

- Linear discriminant analysis
- Why?
  - Simple and may be sufficient
- How?
  - Used a genetic algorithm to search for descriptor subsets
  - Finally used a 6-descriptor model
- Accuracy
  - On the whole dataset, 72%
  - On TSET/PSET, 72% / 71%
  - With leave-10%-out, 71%

Predictive Models

- Random Forest
- Why?
  - No feature selection required
  - Does not overfit
  - May capture non-linearities
- How?
  - Used 500 trees
  - Sampled 6 features at each split
- Accuracy
  - On the whole dataset, 72%
  - On TSET/PSET, 75% 70%



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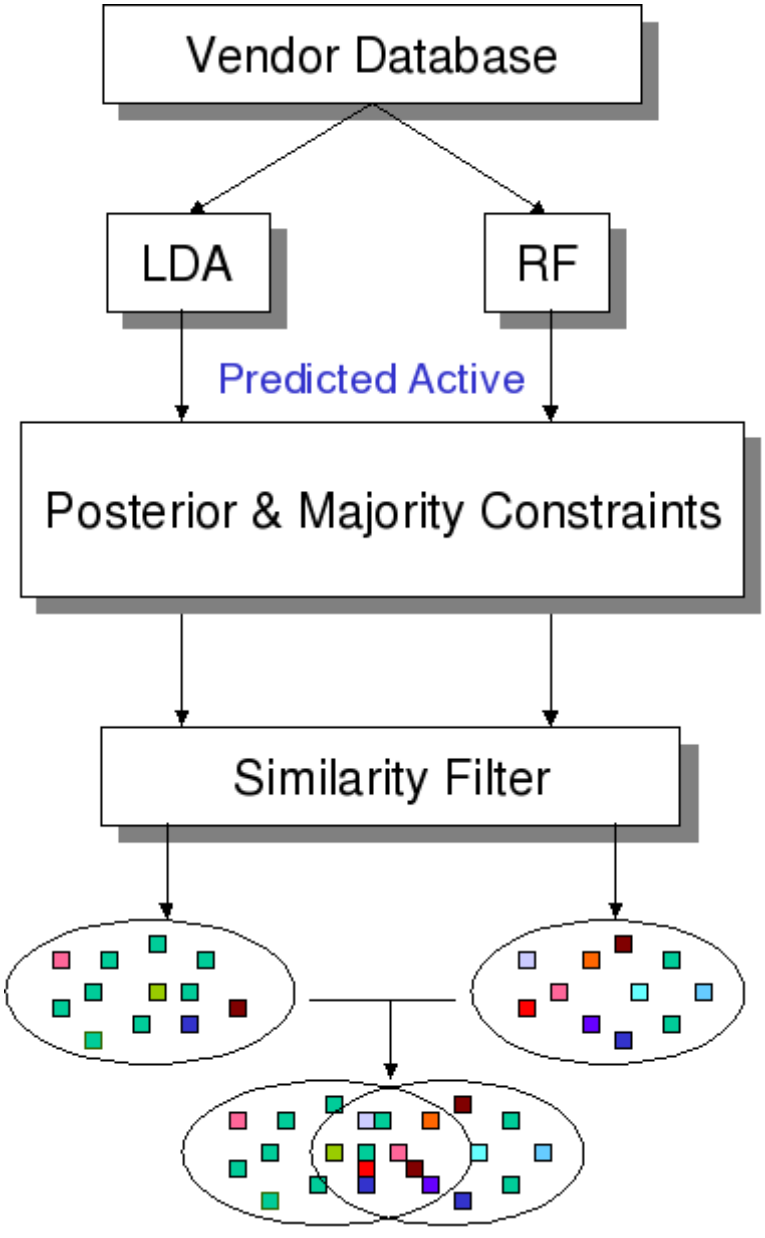
Consensus Predictions

- We first consider compounds predicted active by both models
  - For the LDA model we consider compounds with a posterior $>$ P
  - For the RF model we consider compounds which had a majority $>$ M
- We then apply the similarity filter
- This results in two hit lists
- A final hit list is obtained from the intersection of the hit lists for the individual model



Similarity Filter

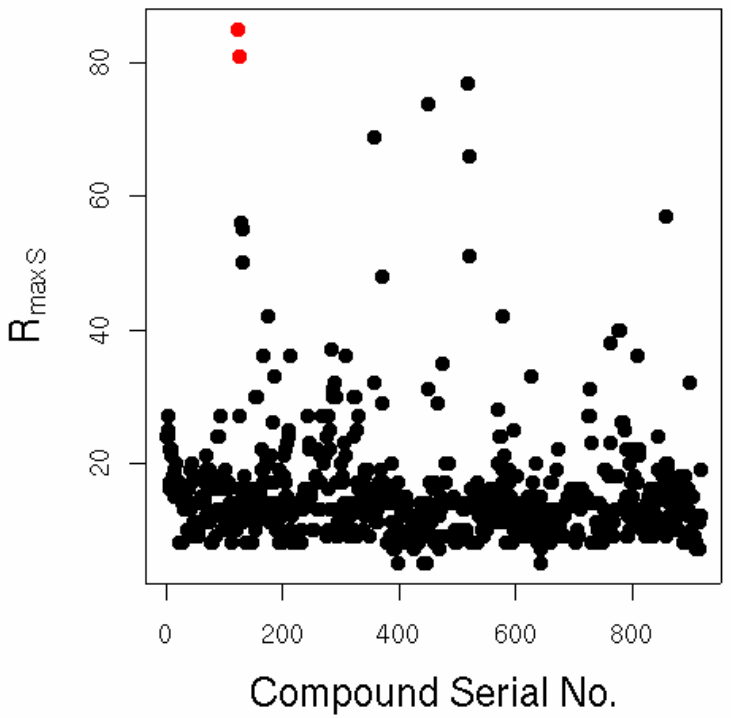
- The goal is to predict actives from the vendor database
- Evaluate 166 bit MACCS fingerprints
- The Tanimoto Similarity between two compounds is defined by

$$S = \frac{N_c}{N_a + N_b - Nc}$$

- For a compound predicted active
  - Calculate average similarity to TSET actives (S_1)
  - Calculate average similarity to TSET inactives (S_2)
  - Select compounds where $S_1 - S_2 \geq \epsilon$

Suggesting Good Leads

- Suggest further prioritization?
  - Look for TSET actives that are not in the bulk of the dataset
  - These compounds may be good starting points for further modifications
  - Evaluate similarity of the hit list compounds to these isolated TSET compounds
- Hit list compounds most similar to the most isolated TSET active may be good leads



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Guha, R.; Dutta, D.; Jurs, P.C; Chen, T.; *J. Chem. Inf. Model.*, **2006**, *46*, 1713–1722

Time Considerations

- Model development
  - Descriptor calculation is rapid and a one time event
  - Building individual LDA or RF models is fast
  - Time required to obtain optimal model can be large when a GA is used (partly due to interpreted code)
  - Predictions for 50,000 compounds $<$ 1min
- Similarity calculation is very time consuming
- Detecting spatial outliers is slow
  - Can be improved with approximate NN algorithms

Dutta, D.; Guha, R.; Jurs, P.C.; Chen, T.; *J. Chem. Inf. Model.*, **2006**, *46*, 321–333

Results

- Parameters
  - P, M > 0.7
  - $\epsilon \geq 0.01$
- Of the 34 hits, 7 have a similarity greater than 0.5 with the most outlying TSET active
- We obtained 66 more hits from an ensemble of LDA models

- LDA - 313 hits
- RF - 57 hits
- Consensus - 34 hits

Average similarity $= 0.64$

None were in common with pharmacophore predictions

Results

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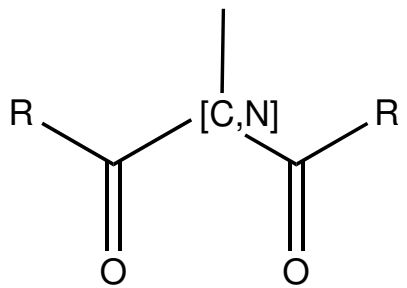
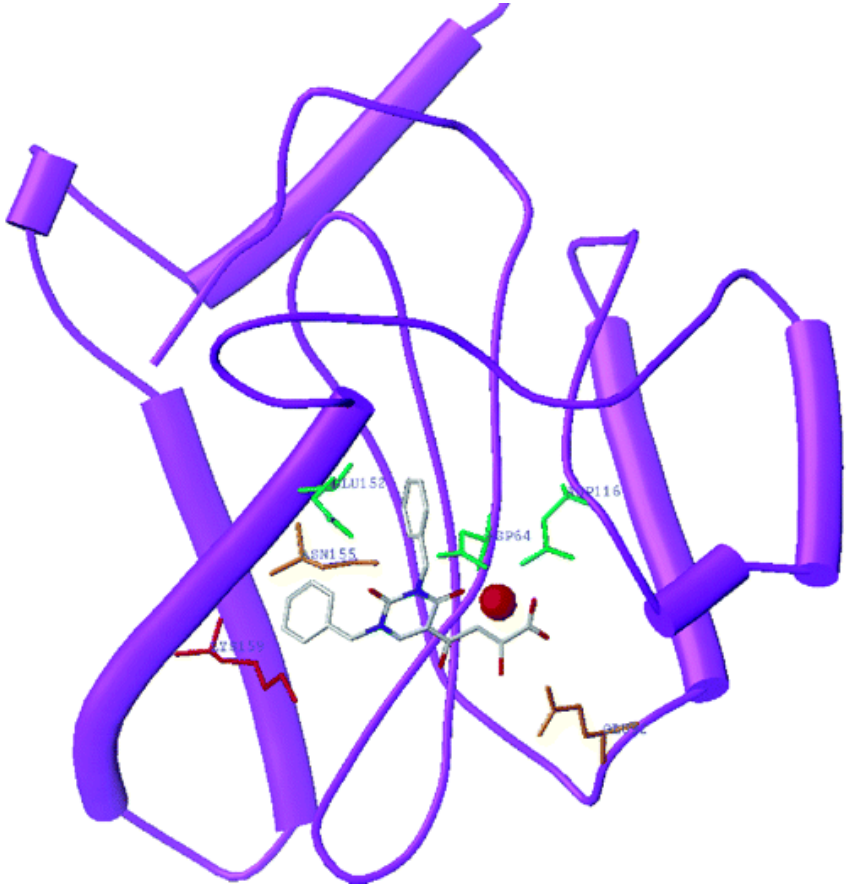
The Search for β diketones

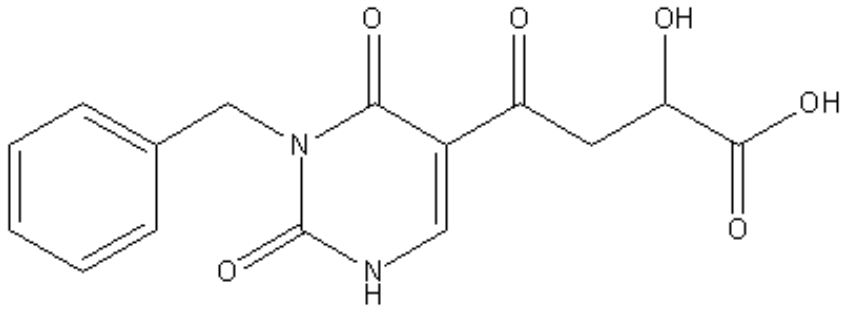
- A recently published inhibitor exhibited a β diketone moiety
- Searched the vendor DB for structures with this feature and predicted them
  - LDA model : 244 actives (posterior > 0.8)
  - RF model : 4 actives (score > 0.85)
  - The intersection set contained 4 compounds
- We missed these hits due to our similarity constraints being too strict



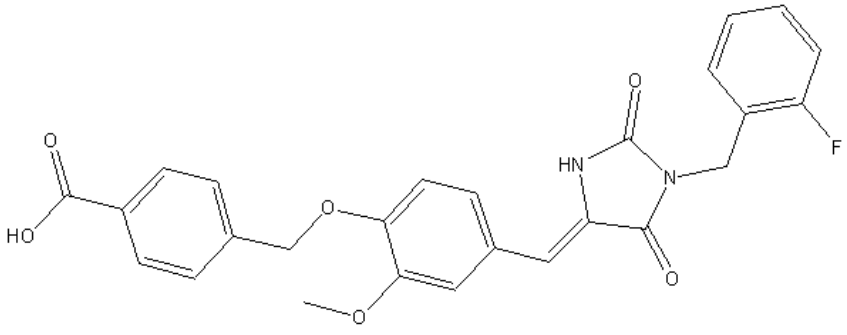
Nair, V.; Chi, G.; Ptak, R.; Neamati, N.; *J. Med. Chem.*, **2006**, *45*, 445–447

Similarity to the Published Compound





Published



Predicted

Future Work

- Investigate similarity to known inhibitors in terms of pharmacophore similarity
- Dock our best hits (may not be conclusive)
- Investigate the distribution of vendor compounds in descriptor space
- Cluster the vendor database and predict representative members of clusters
- Perform assays

Conclusions

- A consensus approach to predictive models allows us to increase confidence in activity predictions
- Prioritization based on similarity is intuitive, but may not work well with homogenous datasets
- The protocol appears to have identified possible leads which await confirmation

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