

# SimFinder: A Unique Topology- based Approach to Similarity Searching

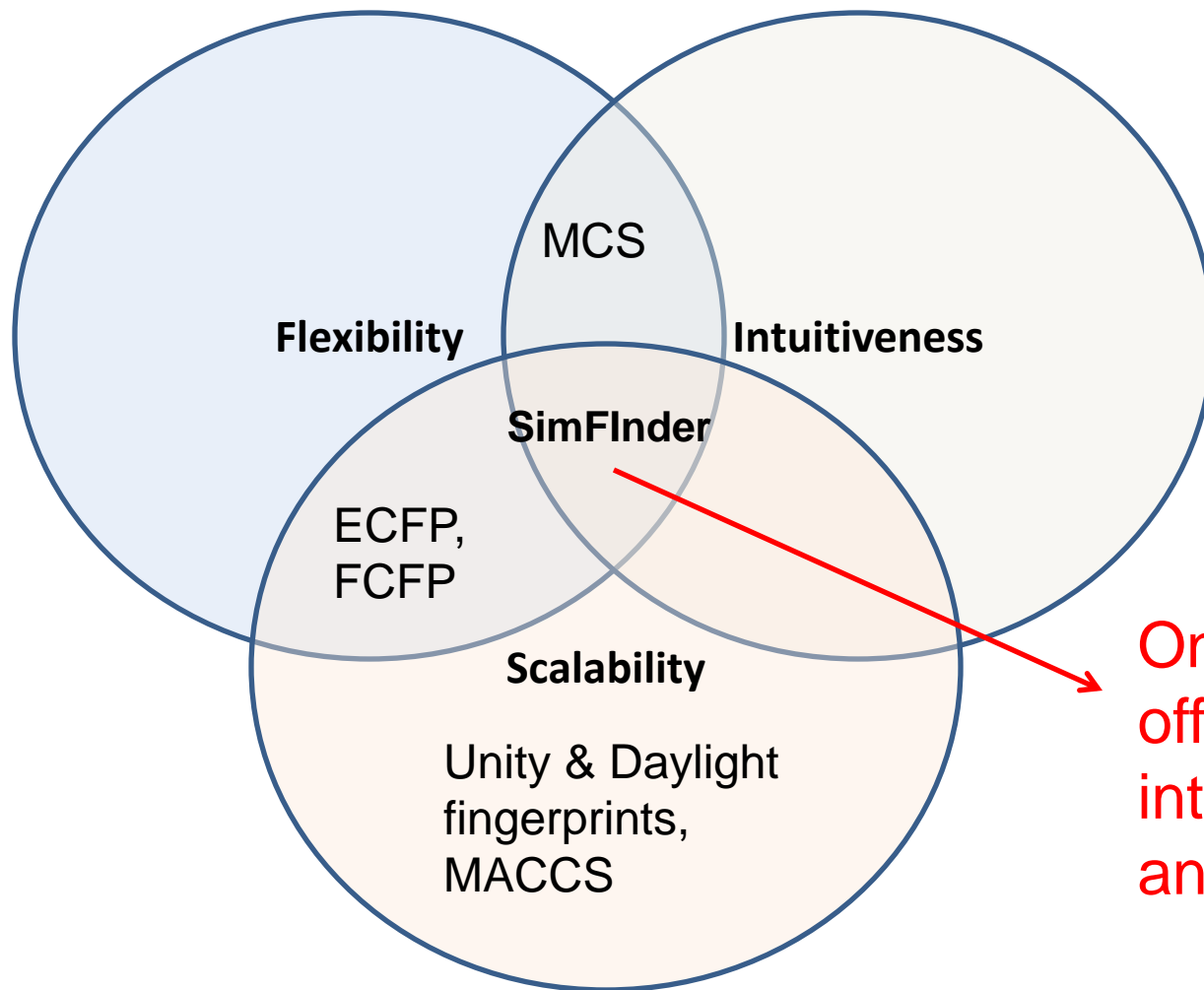
# SimFinder

- Topology-based similarity search
- Flexibility
  - Parameterized similarity measure
  - User-defined functional group abstractions
- Scalability using index structure
  - One-to-many comparisons at a time between query compound and database compounds
    - Alternative techniques rely on one-to-one comparisons

# Applications of SimFinder

- Better diversity analysis of databases
  - Topology reveals unique insights
- Functional group abstractions
  - User-directed
- User can define graph attributes (e.g., types of covalent & non-covalent bonds).
- Ligand-protein interactions can be defined & queried.

# Key Benefits



Only technology offering flexibility, intuitive searches, and scalability

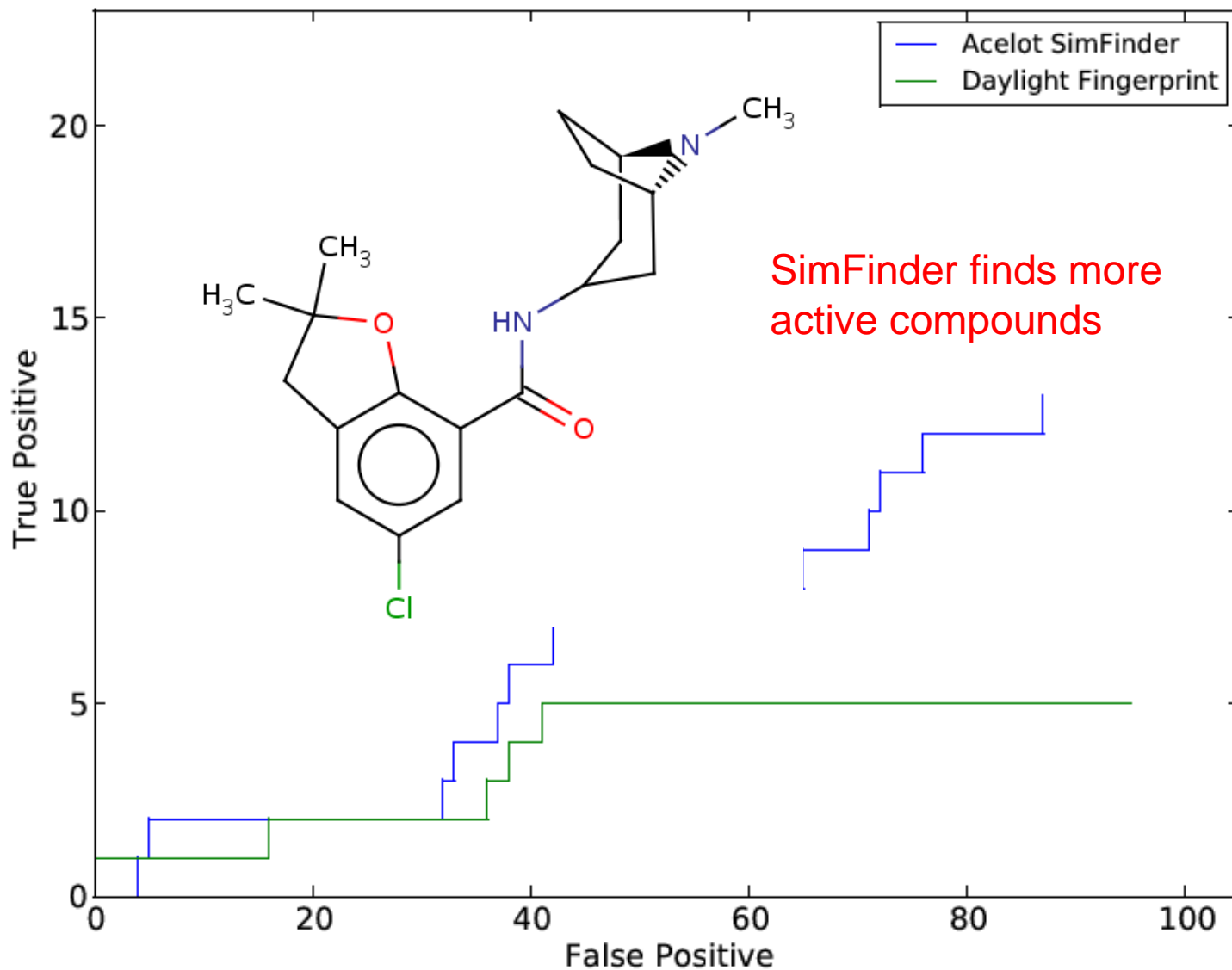
# Retrospective Validation

- Briem & Lessel compound library
- 957 compound subset MDL Drug Data Report (MDDR) classified by biological activity

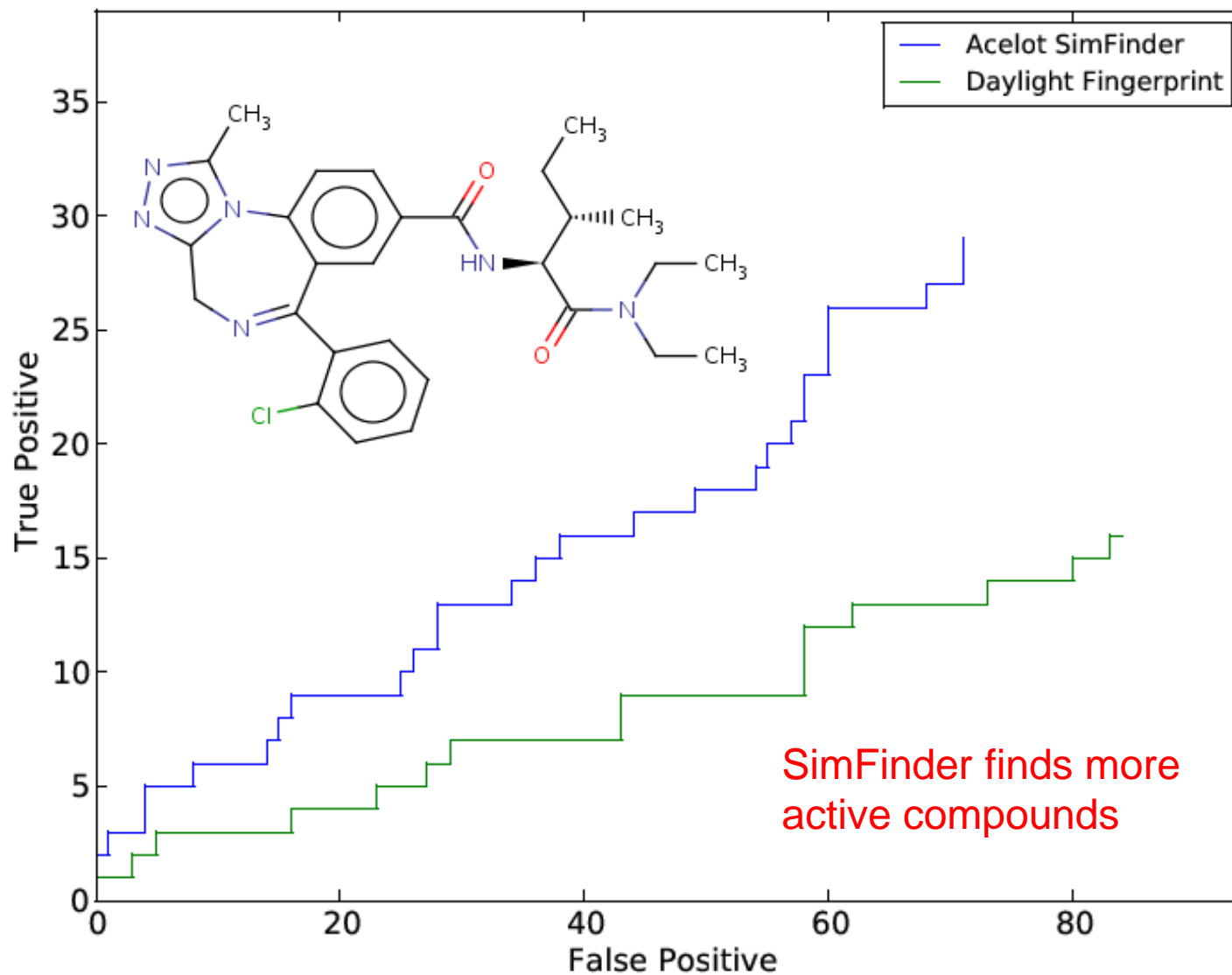
49	5HT3 Re-uptake Inhibitors
40	ACE Inhibitors
111	HMG-CoA Inhibitors
134	PAF Antagonists
49	TXA2 Antagonists
574	"Inactives"

- Query result enriched in the biological activity of the query compound.

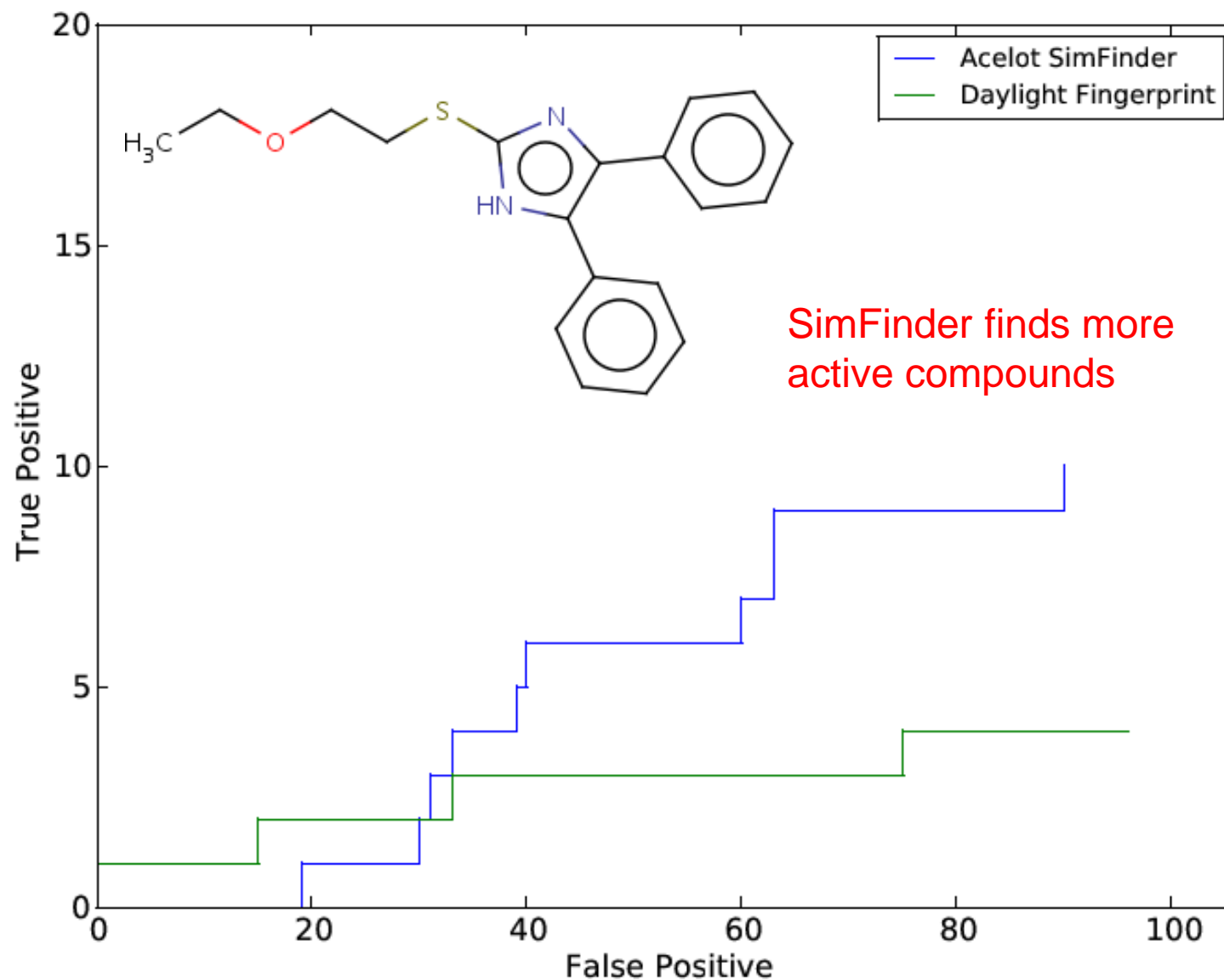
# Serotonin Re-uptake Inhibition



# Platelet Activating Factor



# Thromboxane A2 Antagonist



# BACE-1 & BBB Permeability Studies

- ChemBridge library filtered to remove reactive functional groups + Acelot Blood Brain Barrier permeability filters
- Acelot SimFinder queries on curated library with known BACE-1 inhibitors
- Compounds reviewed for medicinal chemistry considerations, ordered, and %-inhibition determined via *in vitro* BACE-1 assay.

# BACE-1 Study

- Query Structures
  - Statines
- Little overlap between GraphSim and Fingerprint similarity search results.
- Leads are
  - low MW
  - fragment-like
  - tractable with respect to Med. Chem.
- Non-statins (hydroxyethylene isostere) in hit list.
  - *SimFinder* search yields unique compounds and not "more-of-the-same".

# Summary of Retrospective Studies

- Better than fingerprints via retrospective studies.
- Complementary and unique query methods yield complementary and unique drug leads.
  - novel view of sample bank
  - new structural class of drug lead
  - topological approach yields unique structural classes of drug-leads for a given target class.
  - Chemical space explored is complementary to fingerprints or other non-topology based methods

# References

- Huahai He; Ambuj K. Singh; Closure-tree: An Index Structure for Graph Queries. Proceedings of the 22nd International Conference on Data Engineering (ICDE), April, 2006, pp 38 - 50 [DOI :10.1109/ICDE.2006.37](https://doi.org/10.1109/ICDE.2006.37).
- Hans Briem and Uta F Lessel, Perspect. Drug Discov. Dec. 2000 (20), 231-244.