ChemClusterPL

Efficient searching of large chemical databases

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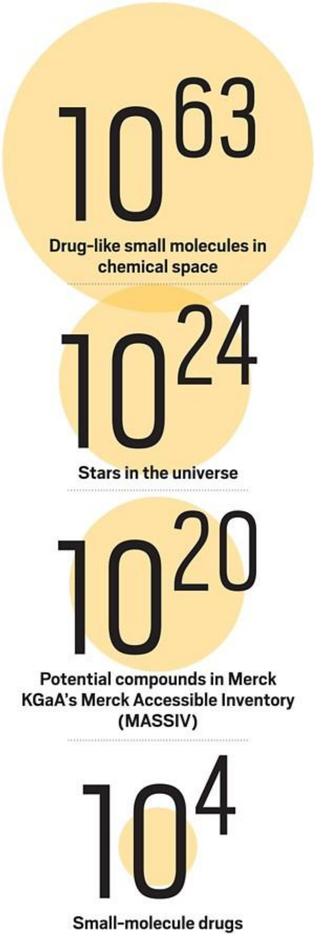
Introduction



The need for rapid search for analogues of existing drugs

Project Idea ??

Google for Molecules: Fast, Smart, Scalable

Goal: Enable fast search and grouping of similar molecules in large databases (e.g., ZINC22)

Our proposal:

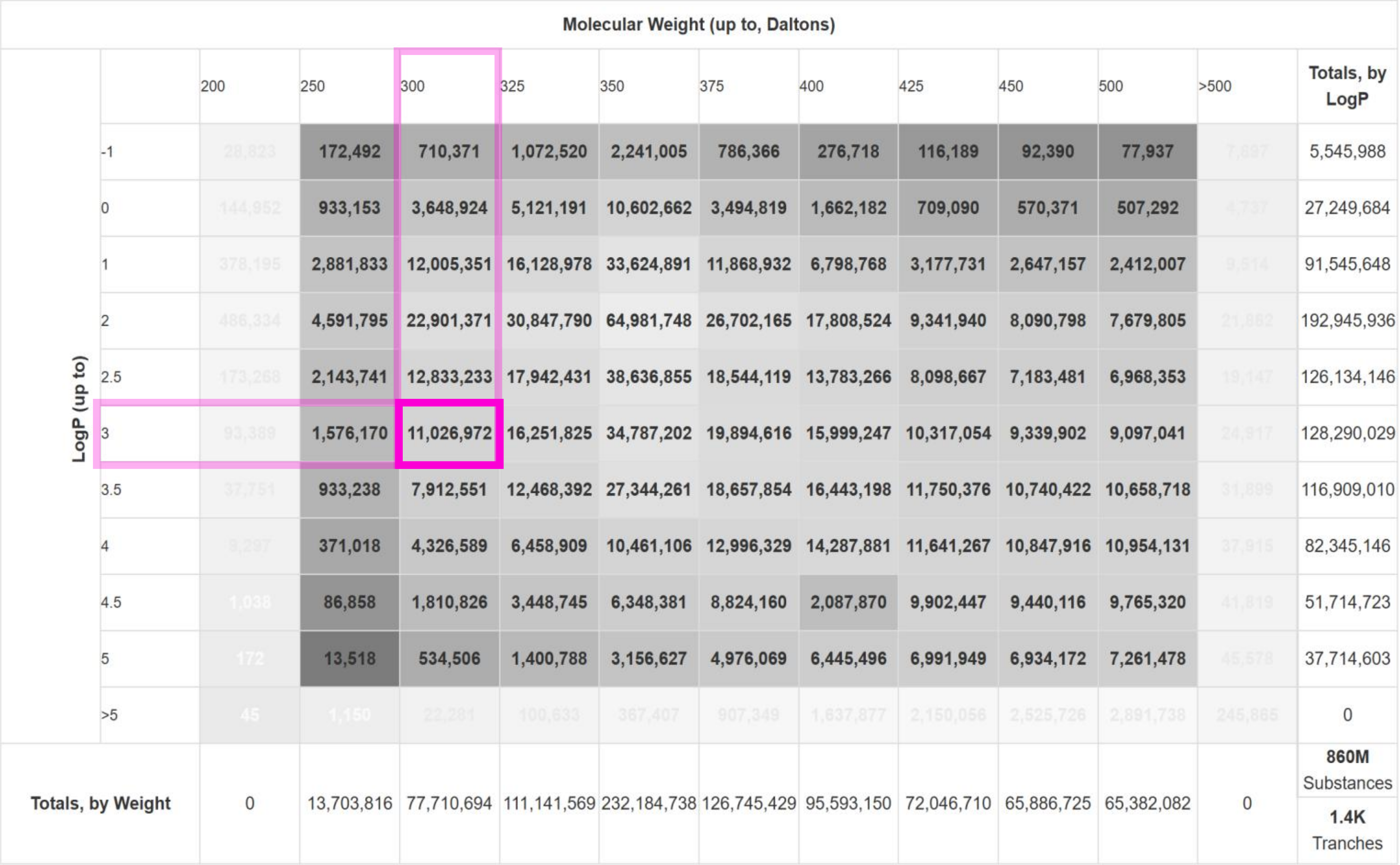
- Scalable similarity search using molecular embeddings
- Fast approximate search
- Clustering at scale

ZINC freely accessible repository of commercially available compounds

ZINC
Data Base

Compounds Selected by:

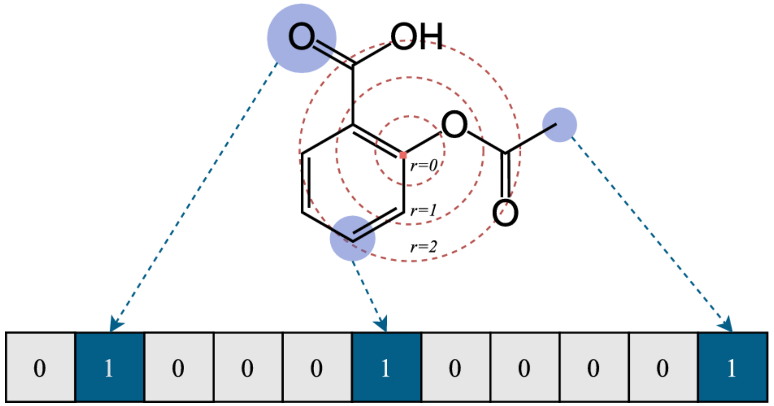
- Availability Type
- Chemical and Pharmacophore Properties
- Structure Format
- Physicochemical Filters



	Molecular Weight (up to, Daltons)											
LogP (up to)	200	250	300	325	350	375	400	425	450	500	>500	Totals, by LogP
-1	28,823	172,492	710,371	1,072,520	2,241,005	786,366	276,718	116,189	92,390	77,937	7,697	5,545,988
0	144,952	933,153	3,648,924	5,121,191	10,602,662	3,494,819	1,662,182	709,090	570,371	507,292	4,737	27,249,684
1	378,195	2,881,833	12,005,351	16,128,978	33,624,891	11,868,932	6,798,768	3,177,731	2,647,157	2,412,007	9,514	91,545,648
2	486,334	4,591,795	22,901,371	30,847,790	64,981,748	26,702,165	17,808,524	9,341,940	8,090,798	7,679,805	21,862	192,945,936
2.5	173,268	2,143,741	12,833,233	17,942,431	38,636,855	18,544,119	13,783,266	8,098,667	7,183,481	6,968,353	19,147	126,134,146
3	93,389	1,576,170	11,026,972	16,251,825	34,787,202	19,894,616	15,999,247	10,317,054	9,339,902	9,097,041	24,917	128,290,029
3.5	37,751	933,238	7,912,551	12,468,392	27,344,261	18,657,854	16,443,198	11,750,376	10,740,422	10,658,718	31,899	116,909,010
4	9,297	371,018	4,326,589	6,458,909	10,461,106	12,996,329	14,287,881	11,641,267	10,847,916	10,954,131	37,915	82,345,146
4.5	1,038	86,858	1,810,826	3,448,745	6,348,381	8,824,160	2,087,870	9,902,447	9,440,116	9,765,320	41,819	51,714,723
5	172	13,518	534,506	1,400,788	3,156,627	4,976,069	6,445,496	6,991,949	6,934,172	7,261,478	45,578	37,714,603
>5	45	1,150	22,281	100,633	367,407	907,349	1,637,877	2,150,056	2,525,726	2,891,738	245,865	0
Totals, by Weight	0	13,703,816	77,710,694	111,141,569	232,184,738	126,745,429	95,593,150	72,046,710	65,886,725	65,382,082	0	**860M** Substances **1.4K** Tranches

Measures of similarity between chemical compounds

- Fingerprints (ECFP - 1024)

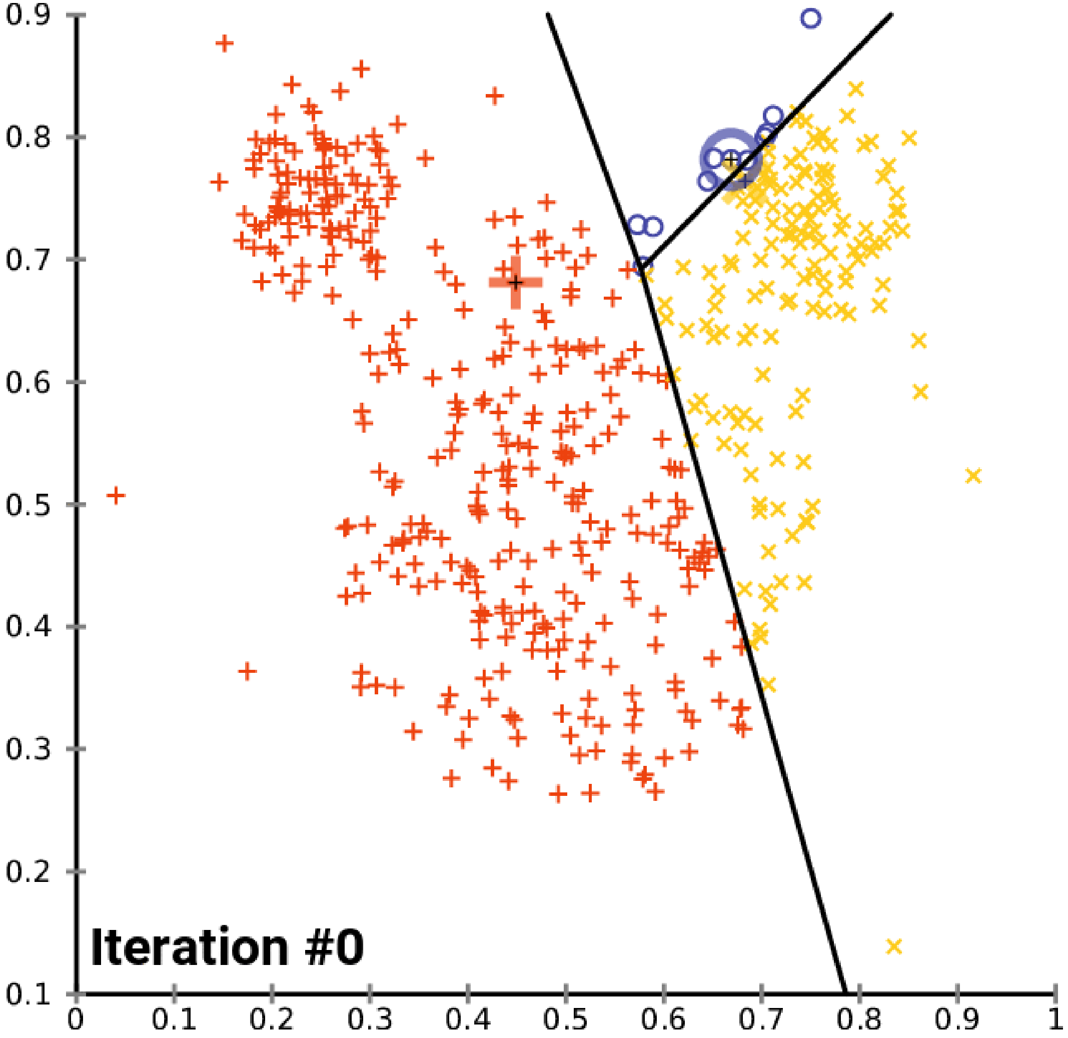


- Tanimoto / Cosine distance

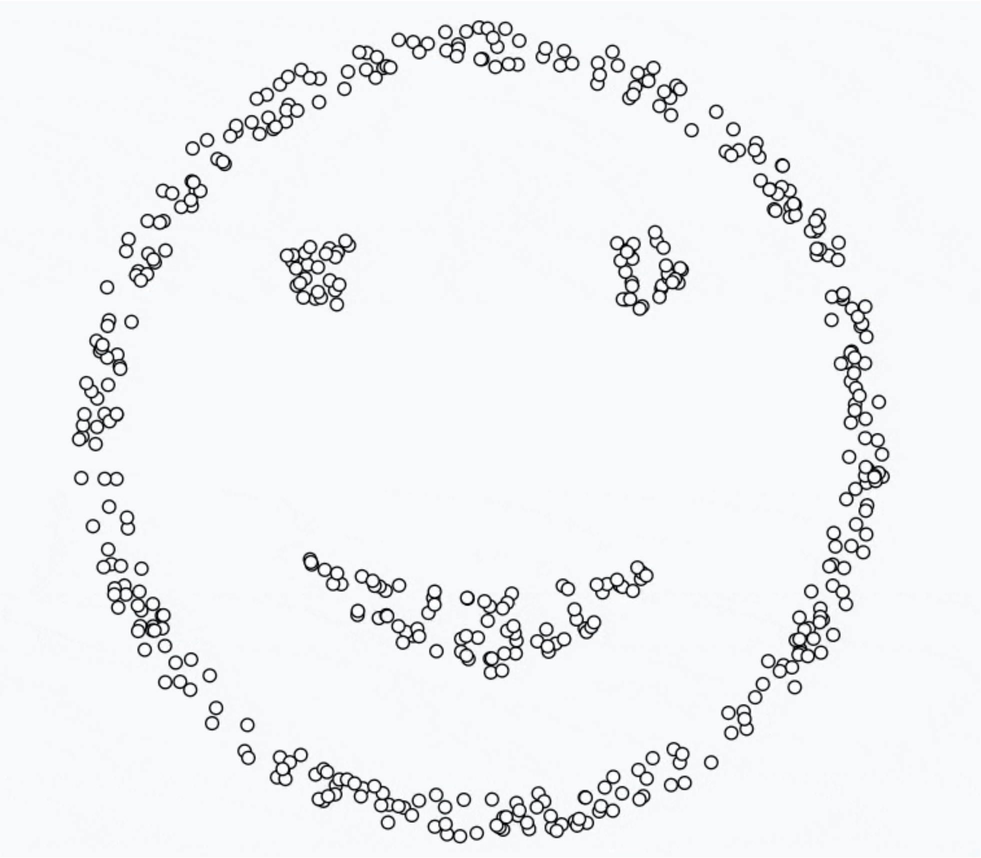
$$T(A,B) = \frac{|A \cap B|}{|A \cup B|}$$

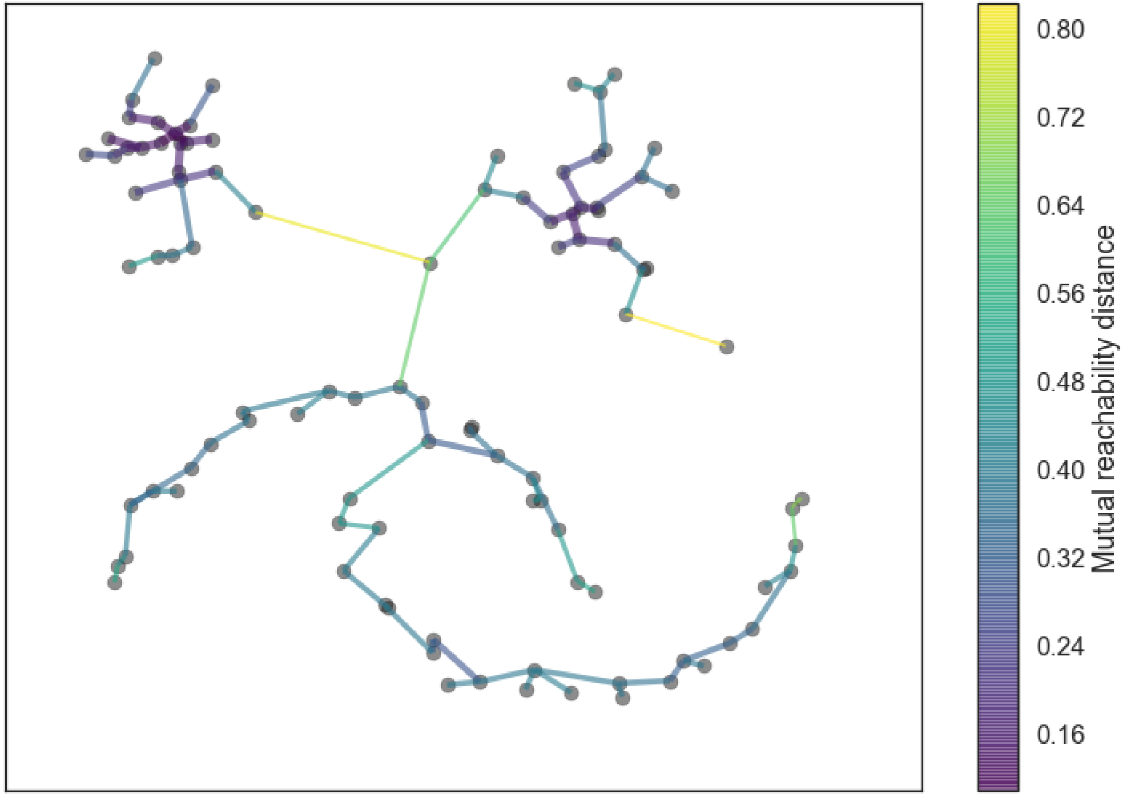
$$\cos(\theta) = \frac{\mathbf{A} \cdot \mathbf{B}}{\|\mathbf{A}\|\|\mathbf{B}\|} = \frac{\sum\limits_{i=1}^{n} A_i B_i}{\sqrt{\sum\limits_{i=1}^{n} A_i^2}\sqrt{\sum\limits_{i=1}^{n} B_i^2}}$$

Clustering methods – K-medoids

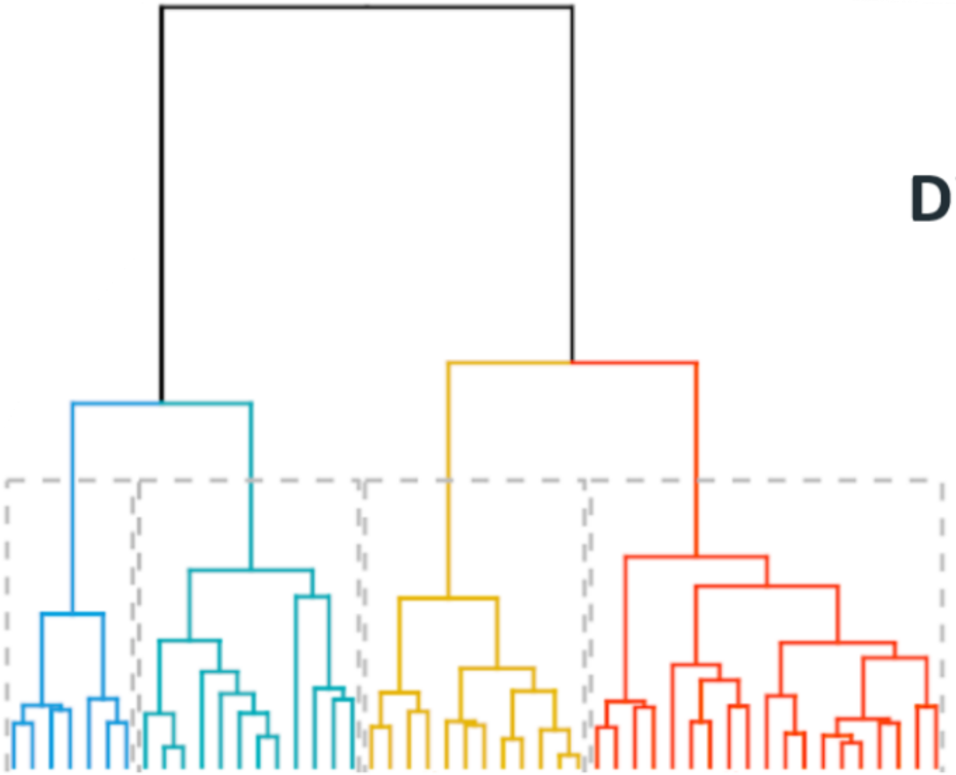


Clustering methods - HDBSCAN



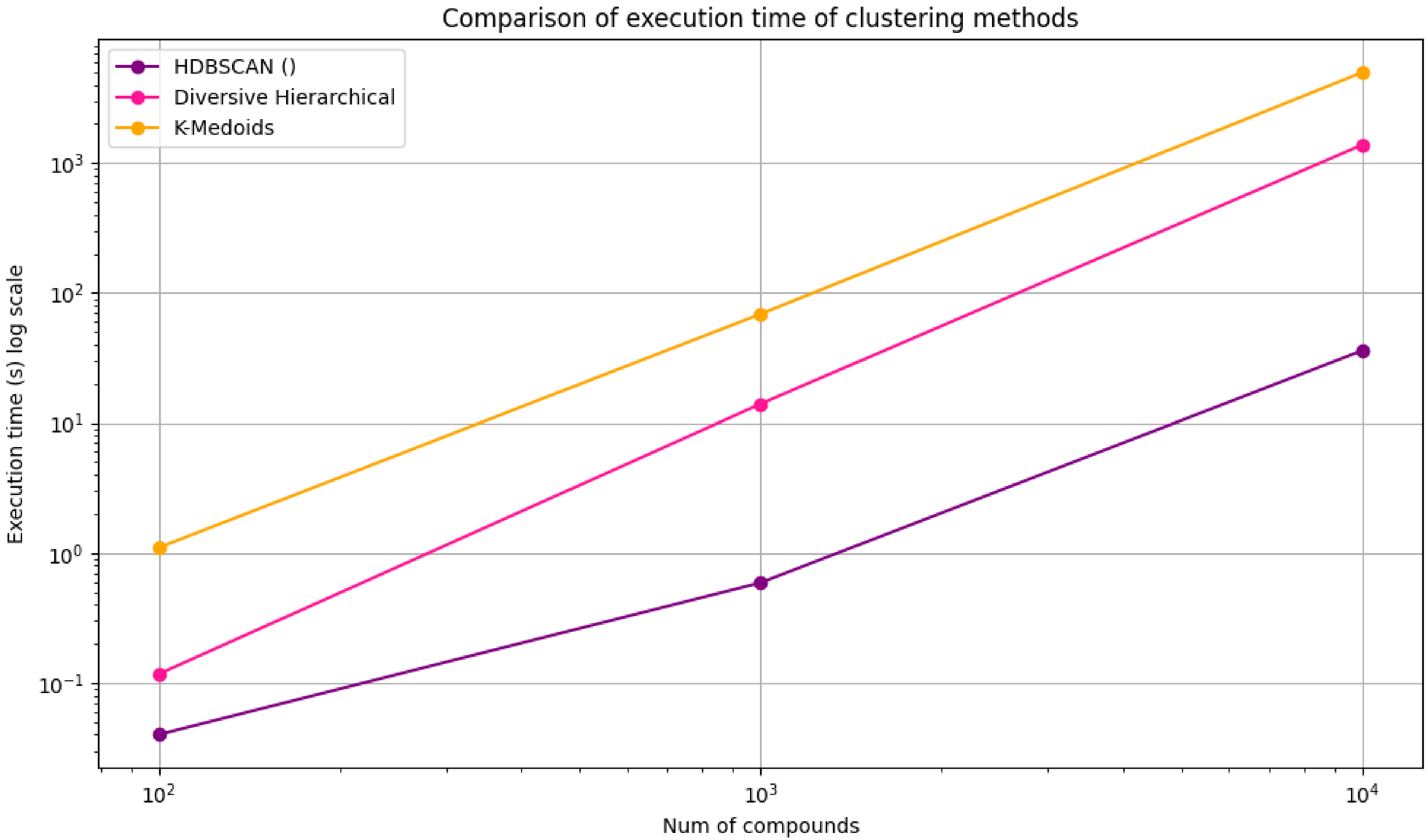


Clustering methods – Divisine hierarchical

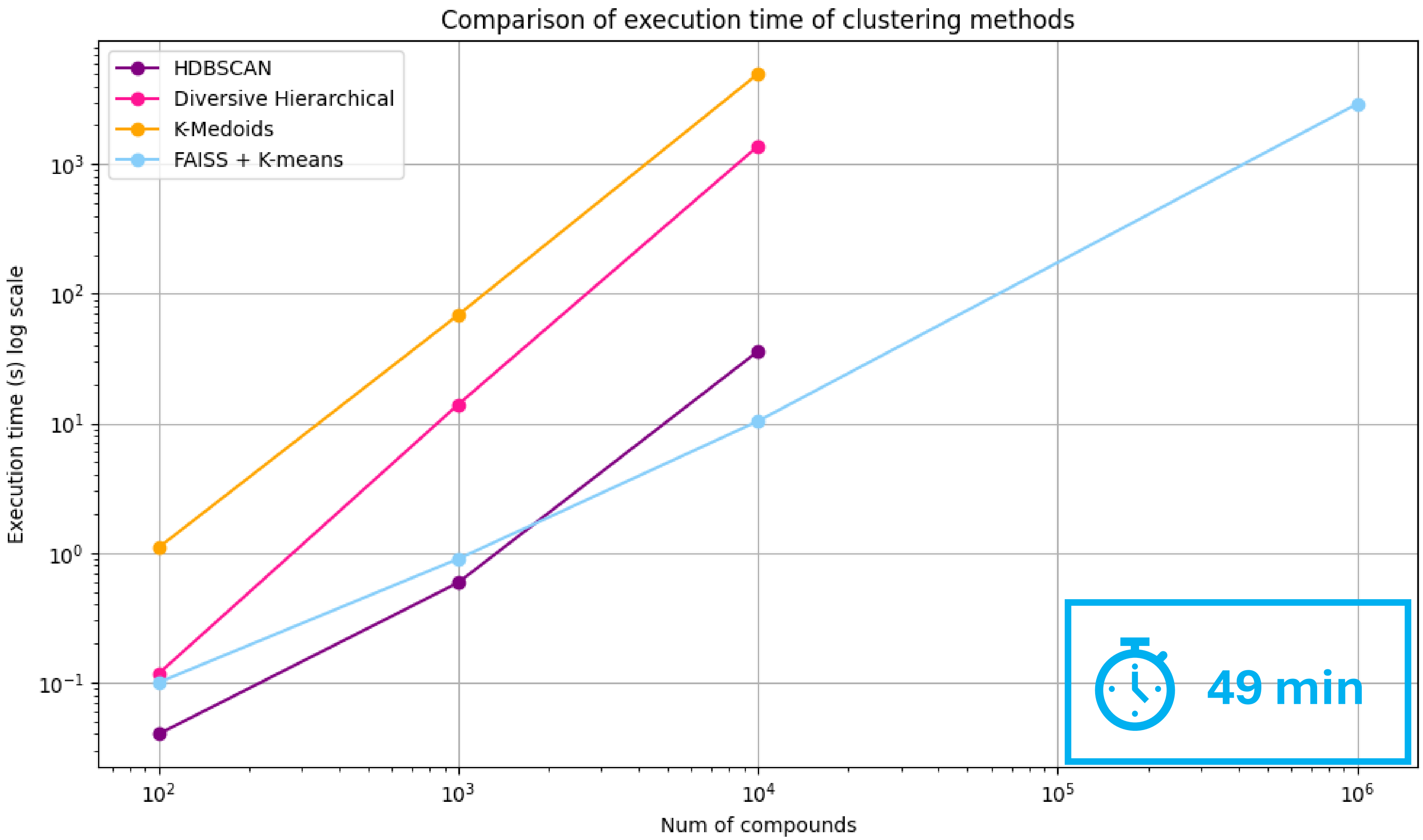


Divisive

Complexity and performance analysis

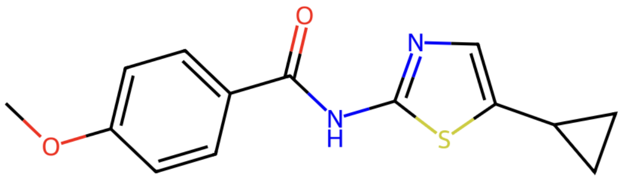


Implementation with FAISS

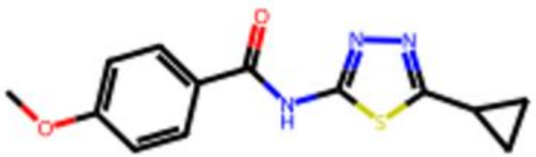


49 min

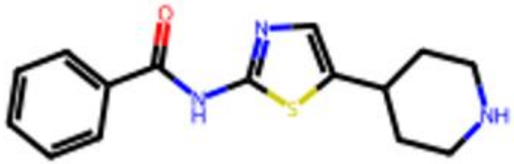
Searching in entire database



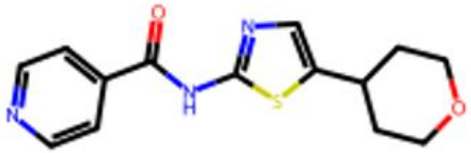
COc1ccc(cc1)C(=O)Nc2ncc(s2)C3CC3



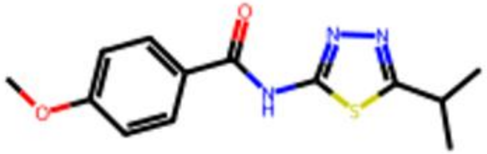
T:0.66 C:0.79



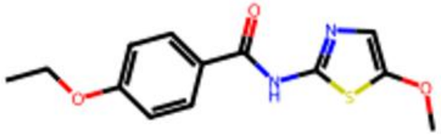
T:0.59 C:0.74



T:0.58 C:0.73



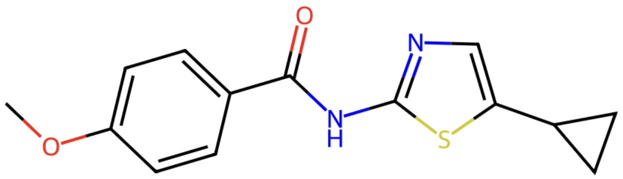
T:0.56 C:0.72



T:0.56 C:0.72

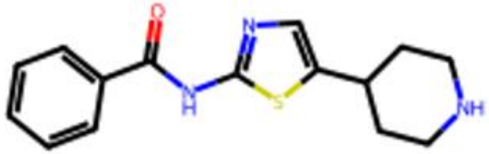
7m 23s

Searching in ChemClusterPL

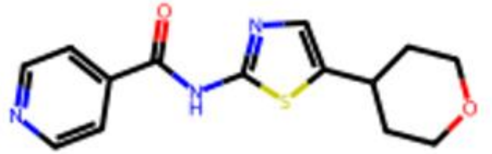


COc1ccc(cc1)C(=O)Nc2ncc(s2)C3CC3

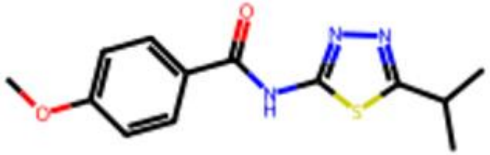
5,424 s



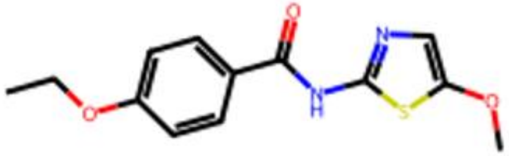
Tanimoto: 0.59 Cosine: 0.74



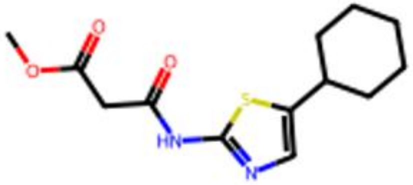
Tanimoto: 0.58 Cosine: 0.73



Tanimoto: 0.56 Cosine: 0.72



Tanimoto: 0.56 Cosine: 0.72



Tanimoto: 0.54 Cosine: 0.70

Balancing cluster sizes

Method	B2 Index
TanimotoNN	0,0010
HDBSCAN	0,0024
FAISS_KMeans	0,1522
SKLearn_KMeans	0,1226
FAISS_Hierarchical	0,0536

Conclusions

- Achieved **high accuracy** in similarity grouping
- Reached **very fast runtimes**, even on large datasets
- Successfully **scaled clustering to databases** that are infeasible using traditional methods (e.g., ZINC22-scale)

Further work

- Deploy solution on **GPUs for even faster performance**
- Extend to **larger datasets** (tens of billions of molecules)
- Integrate with existing **drug discovery pipelines**

Bibliography

https://hdbscan.readthedocs.io/en/latest/how_hdbscan_works.html

https://en.wikipedia.org/wiki/K-means_clustering#:~:text=k%2Dmeans%20clustering%20is%20a,a%20prototype%20of%20the%20cluster.

https://arxiv.org/abs/1702.08734