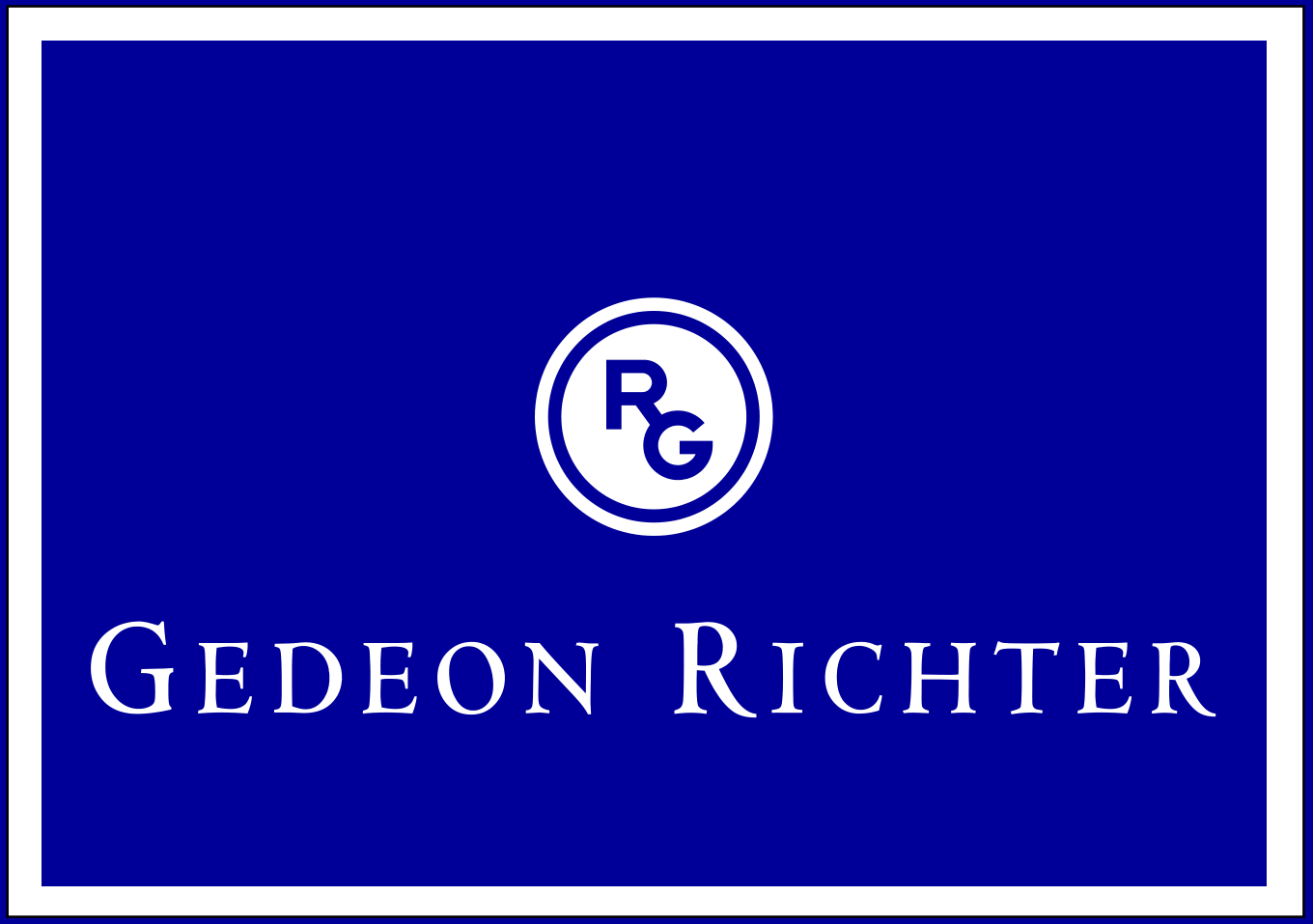

GEDEON RICHTER

Chemaxon tools at Gedeon Richter

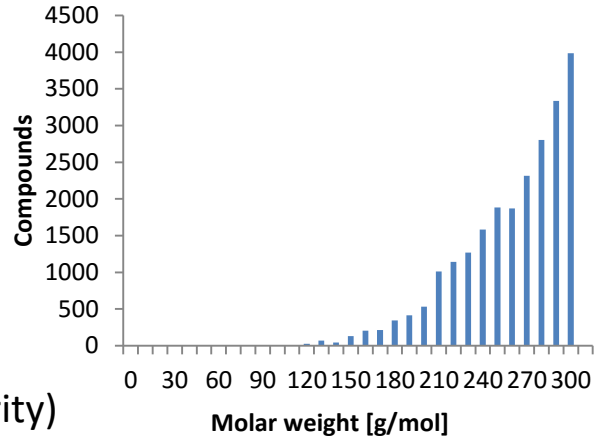
Peter Pogány, Ildikó Magdó, Balázs Krámos
Spectroscopic Research
Gedeon Richter

Cheminformatics at GR

- Aid the synthetic and analytical chemists
  - Data storage (compounds, measured values, spectra)
  - Data retrieval
  - Data analysis (histograms, SAR, regression)
  - Data calculation
  - Similarity, substructure searches
- Aid drug development process: molecular modeling
  - Homology modeling
  - Docking experiments
  - Pharmacophore modeling
- Software from: Chemaxon, ACD/Labs, Schrodinger

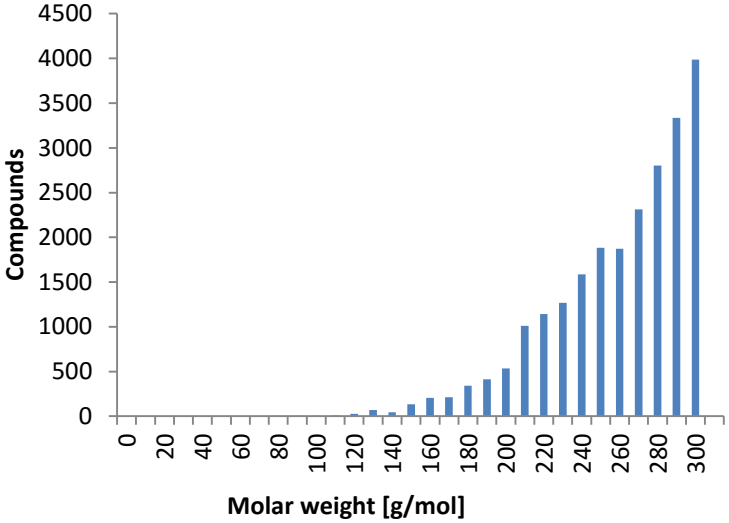
Cheminformatical tools at GR

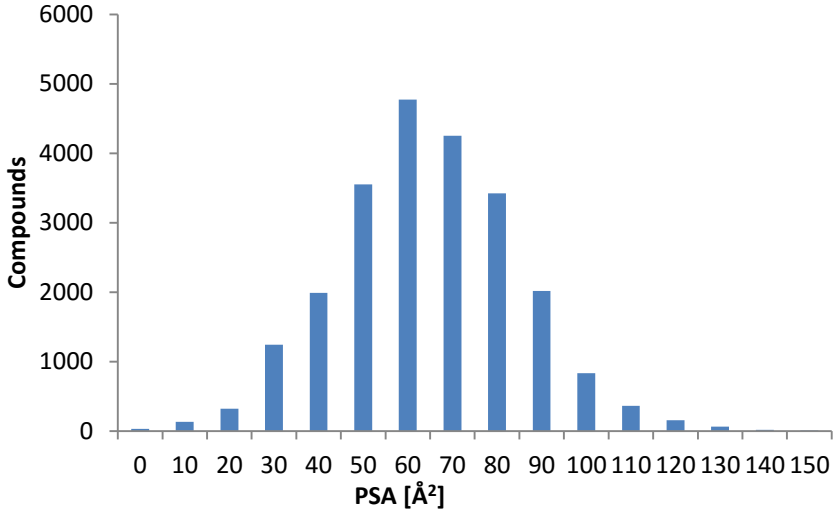
- In-house developed SQL database
  - Reduced databases (for HTS):
    - Fragment database (MW<300)
    - Screening database (high diversity)
  - Compound registration:
    - Purity, integrity (analytical identity + analytical purity)

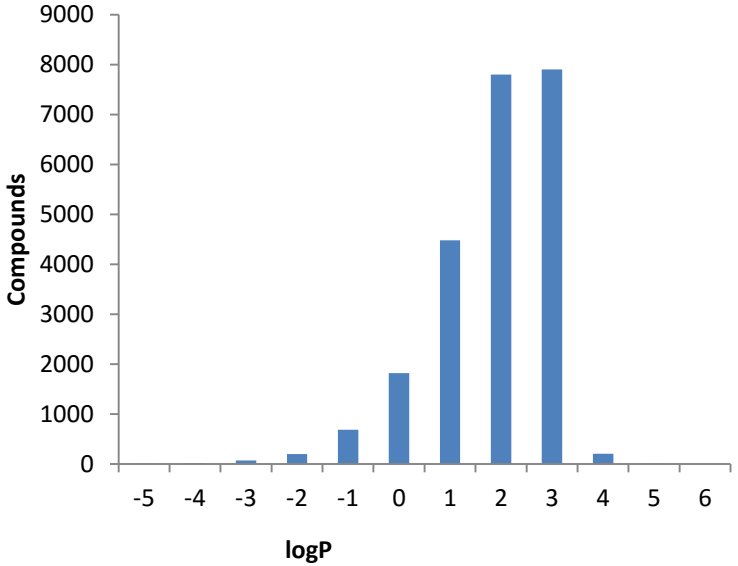


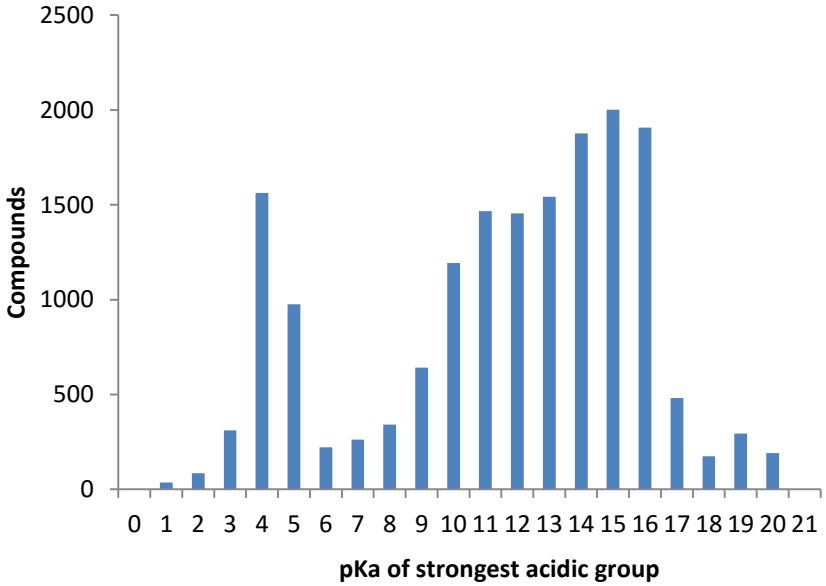
- Seurat – MedChem data analysis
  - visualization/searching application from Schrodinger
- Chemdesk – in-house vendor searching, calculated parameters (ChemAxon), metabolism (SmartCYP), solubility
- MarvinLive (under testing)
  - „Chemical chat" application from ChemAxon
- ADMS – analytical data management system (ACD/Labs)

Fragment database



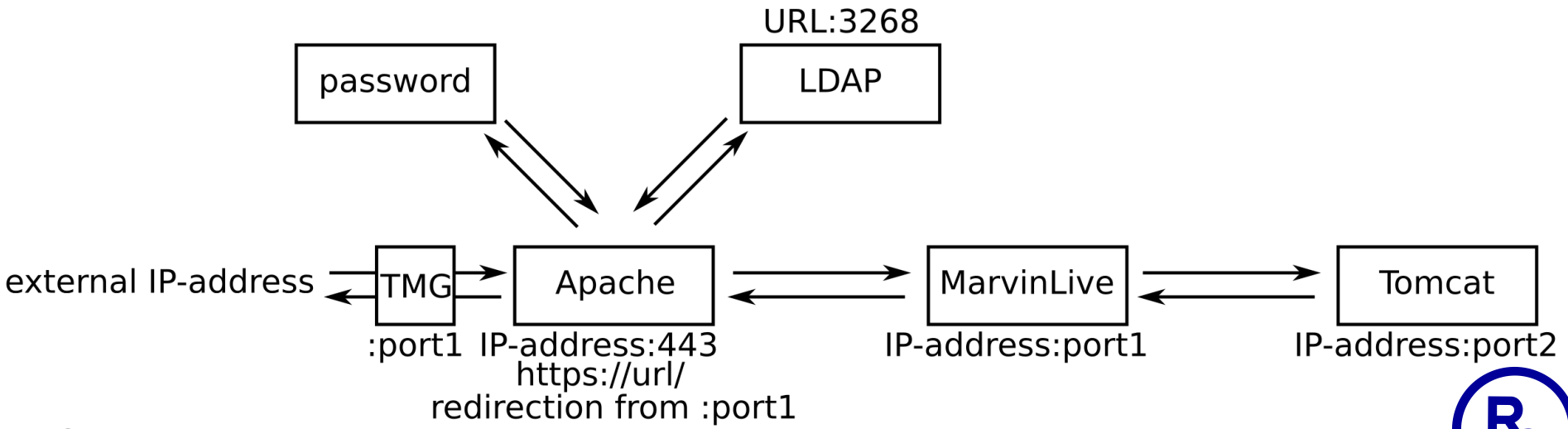




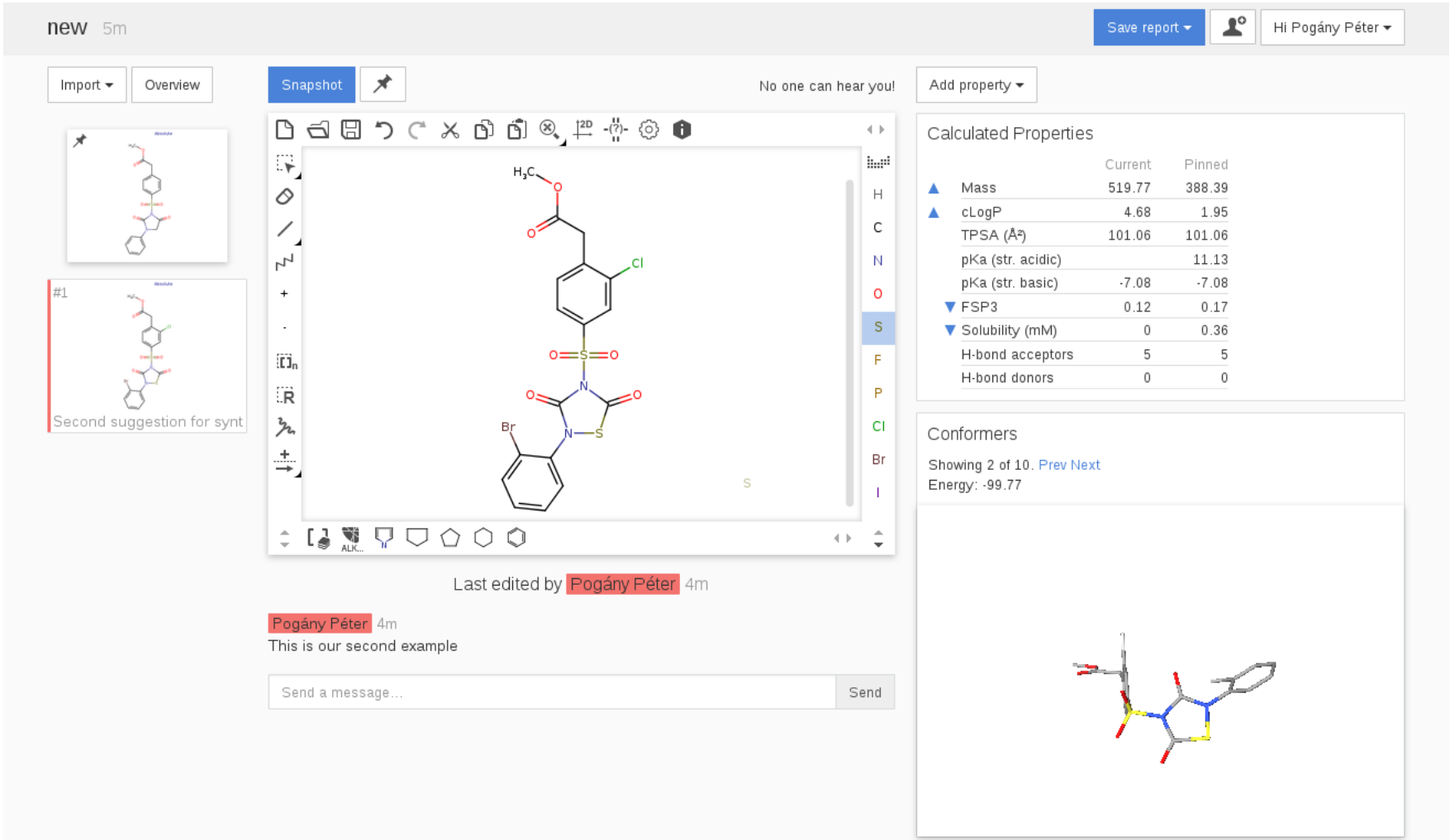


Test of MarvinLive at GR

- New tool under testing – help from the developers
- Security issues
- Positive feedback: easy idea sharing
- npm installation (platform and public registry for sharing JavaScript codes and handling updates): problems with Proxy
- Problem: Dual authentication needed for external - and for internal users (Apache): LDAP & SHA-password file



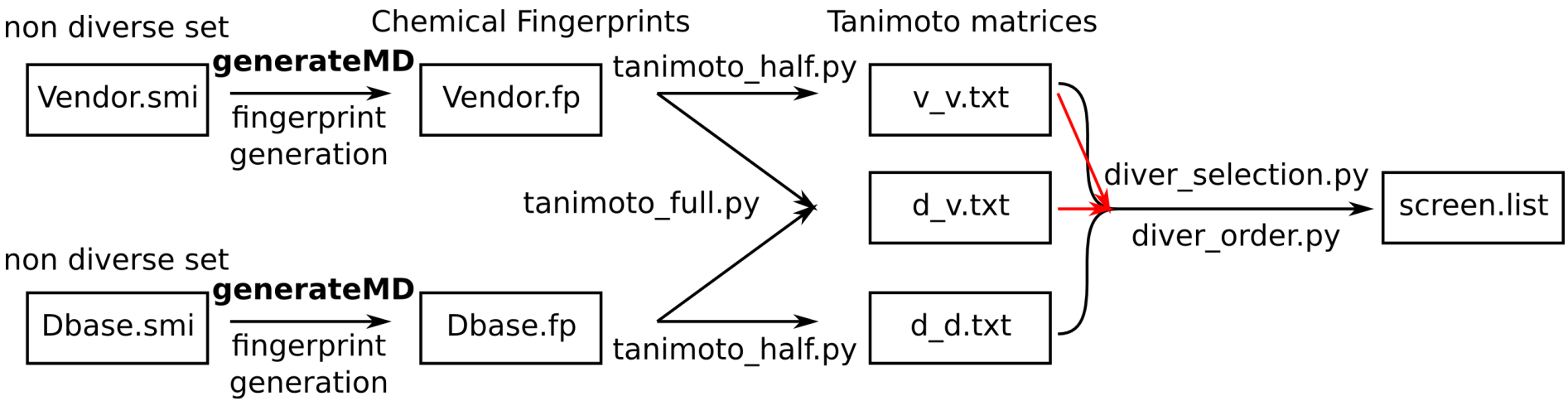
Test of MarvinLive at GR



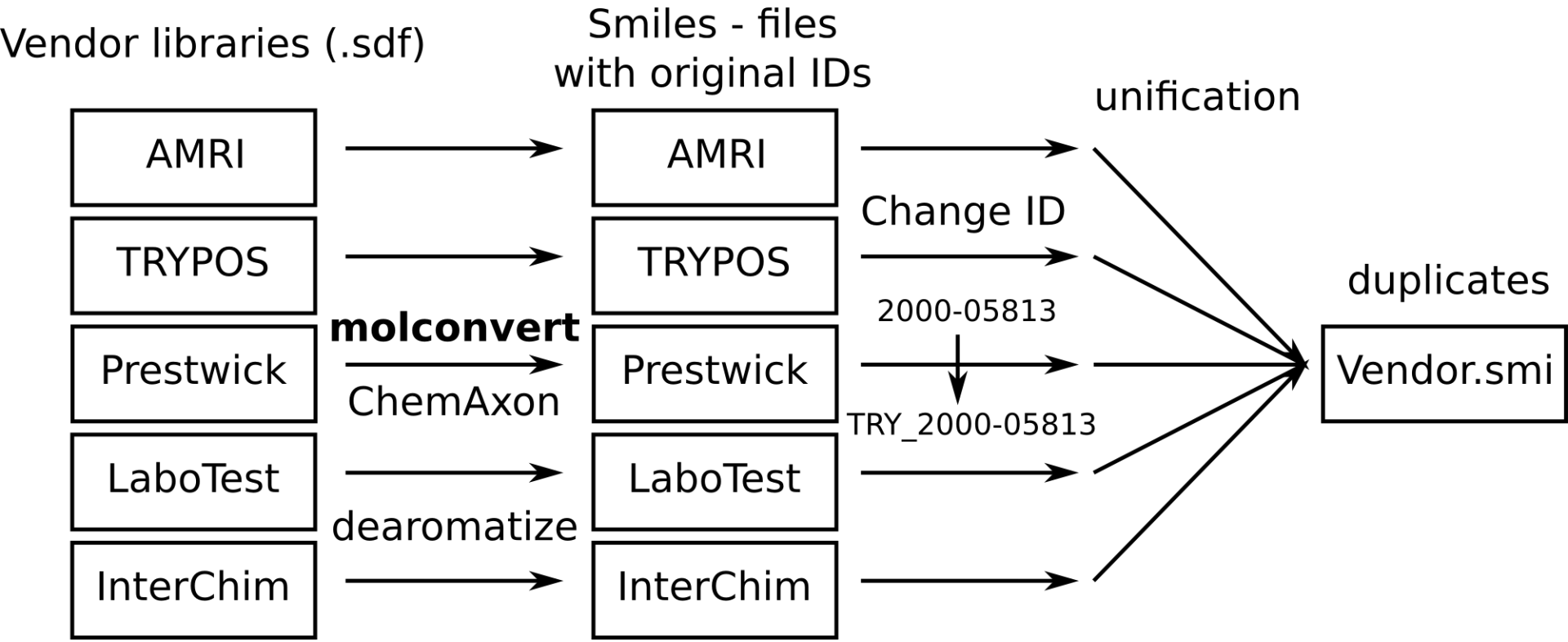
- Future plans: automatic registration of compounds into Seurat ideas table
- ? Downloading data for the compounds from public databases

Screening database (ChemAxon tools)

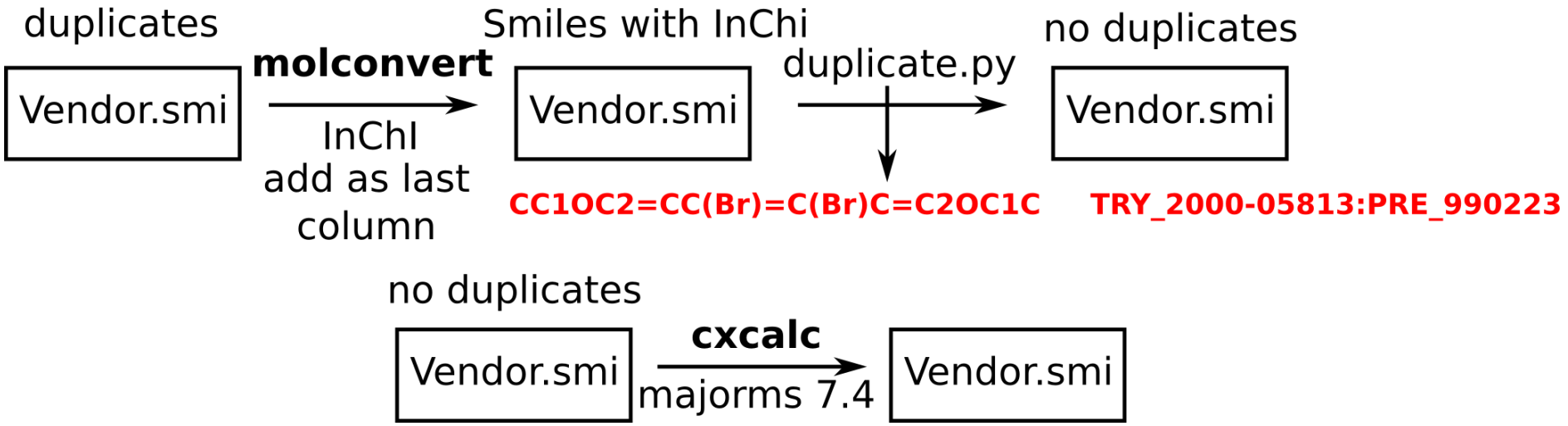
- Aim: Choosing a diverse set of molecules from a bought non-diverse library (list: Vendor.smi) – non-virtual



Vendor Library preparation



Vendor Library preparation

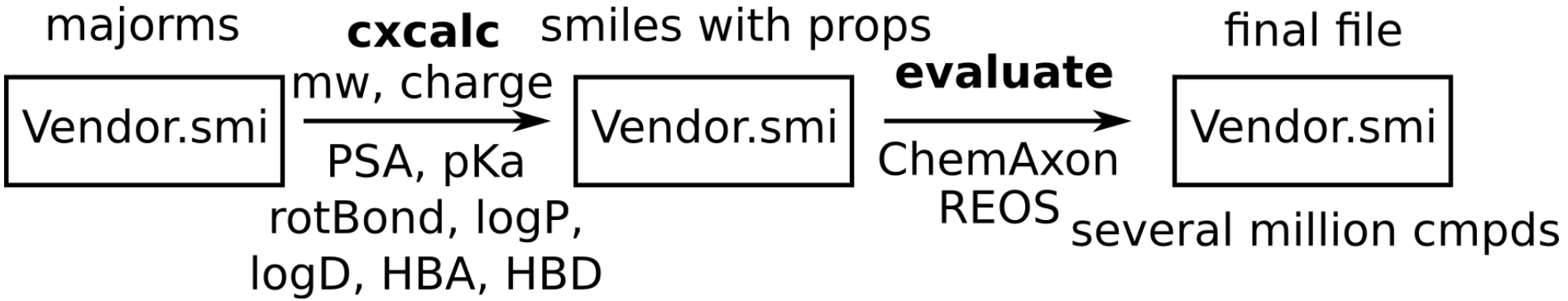


Duplicate filtering – The IDs (with vendor information) are concatenated with „:”

Suggestion: Change duplicate filtering of ChemAxon (only first record is kept; cannot merge data according to structure)

Majorms – Calculates the major microspecies at pH 7.4

Vendor Library preparation



- Future plans: **SQL** database from the vendor library

REOS

- Axerio-Cilies et al., *Eur. J. Med. Chem.*, **44**, 2009, 1128-1134
- Bruns et al., *J. Med. Chem.*, **55**, 2012, 9763-9772
- Davis et al., *Curr. Top. Med. Chem.*, **5**, 2005, 421-439
- Baell et al., J. Med. Chem., **53**, 2010, 2719-2740

Case study (hypothetic) **JKlustor, InstJChem**

- Cysteinyl leukotriene receptor type 1 antagonists with anti-asthma effects
- Let's assume: HTS results gave **135 active** molecules with **IC50<1000 nM**
- After clustering (**JKlustor**): **14** clusters
- Which cluster is it worth to continue the investigations with?

Case study (hypothetic)

Cluster Number	Cluster element no.	Minimum IC50 [nM]
1	1	200
2	1	1.73
3	1	0.8
4	26	0.59
5	1	490
6	2	13
7	18	11
8	35	1.5
9	1	14
10	3	2
11	40	0.19
12	3	3.1
13	1	10
14	2	0.7

- Similarity search in vendor database
- Duplicates removed

Case study (hypothetic)

Cluster Number	Cluster element no.	Minimum IC50 [nM]	No. of similars/element no. at 0.6 Tanimoto
1	1	200	43
2	1	1.73	2
3	1	0.8	7
4	26	0.59	234.9
5	1	490	11
6	2	13	4.5
7	18	11	3.9
8	35	1.5	82.7
9	1	14	9
10	3	2	0.3
11	40	0.19	0.3
12	3	3.1	1.7
13	1	10	2
14	2	0.7	0

Acknowledgements

- István Vágó
- Ákos Tarcsay
- Márton Vass
- László Molnár
- Márk Sándor
- Zoltán Béni

Thank you for your attention