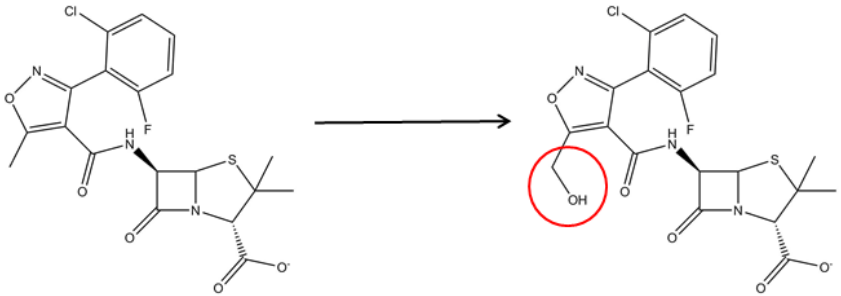
Metabolism Prediction [MetaP]

CS leader: Daan Geerke (VU), **Involved:** UU, JGU, UHH/HITeC

- (Insights into) metabolism of a compound can be important for predictive toxicology and risk assessment



openrisknet.org/e-infrastructure/development/case-studies/case-study-metap

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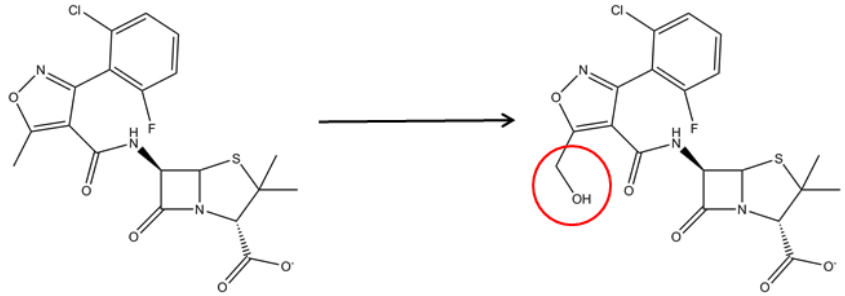
- (Insights into) metabolism of a compound can be important for predictive toxicology and risk assessment
- MetaP: successful Integration of tools to predict (sites of) metabolism (also: third-party, implementation challenge)
- Diverse, complementary tools:
  - Ligand or protein-structure based
  - CYP450 metabolism, phase I, phase II, or combined phase I/II
  - Reaction types (phase I) in addition to site-of-metabolism prediction



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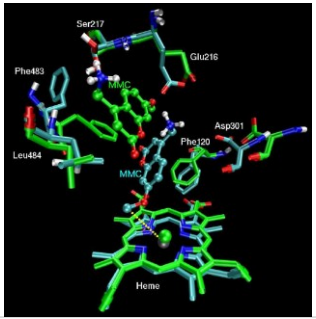
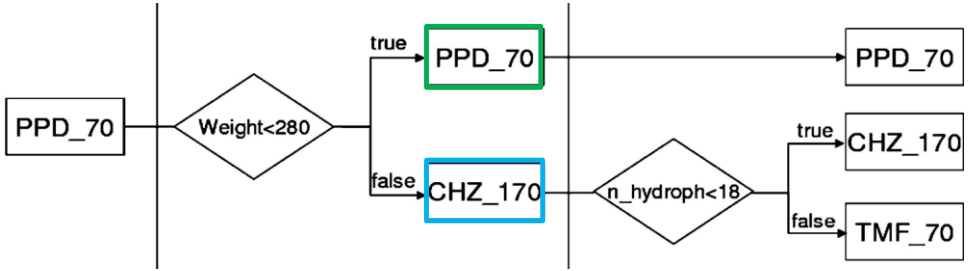
Tools/APIs

- **MetPred:** ranks most probable sites-of-metabolism (SOMs) and reaction types based on similar atom environments and ReactionSMARTS in annotated dataset
- **FAME 3.0**: SOM prediction for phase I, phase II, or combined phase I/II metabolism, from machine learning using 2D-circular-environment based atomic descriptors [implementation challenge]
- **enviPath**: prediction of microbial biotransformation pathways and products using rules represented by SMIRKS (ongoing)
- **SMARTCyp**: SOM prediction for P450 metabolism based on fragment-mapping to pre-computed QM data and atomic accessibility, extended with simple ligand-based pharmacophore rules for specific isoforms
- **Protein-structure based predictors**: plasticity models for docking into (flexible) P450 isoforms

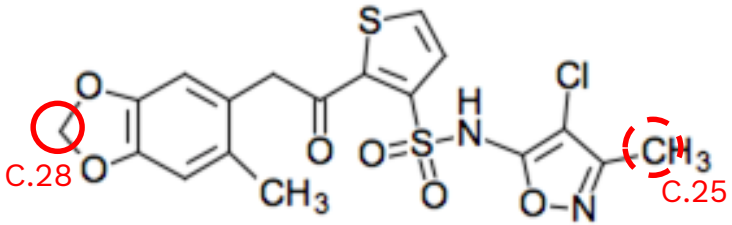




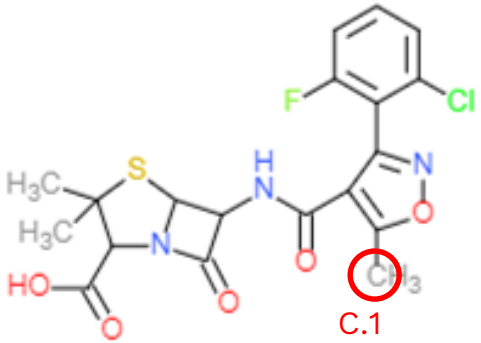
Adapted from Hritz et al. J Med Chem 2008

Jupyter Notebooks: combine and visualize results, used e.g. to explore added value of combined use in a pilot study on 13 drug compounds for which possible metabolite-associated toxicity was previously reported

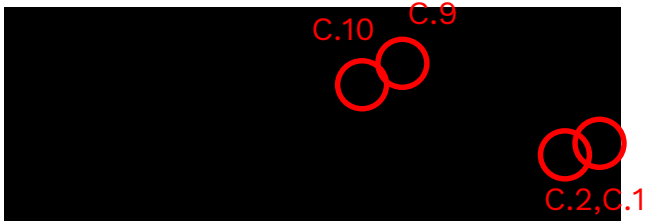
Some pilot study compounds: SOMs



Sitaxentan



Flucloxaxillin



Pioglitazone

Demo

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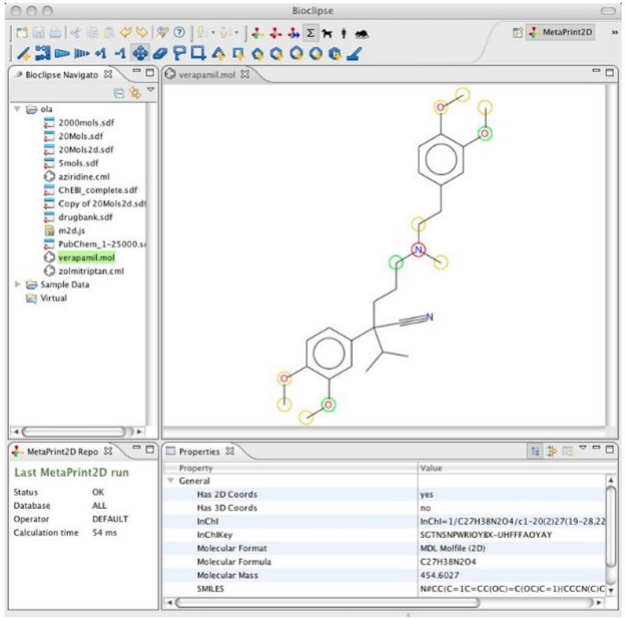
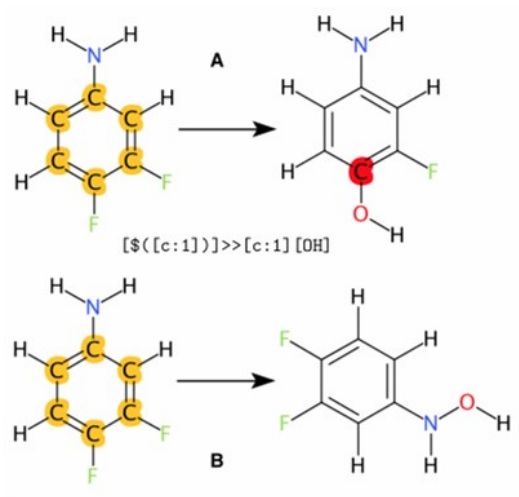
- Diverse, complementary tools:
  - Ligand or protein-structure based
  - CYP450 metabolism, phase I, phase II, or combined phase I/II
  - Reaction types (phase I) in addition to site-of-metabolism prediction
- Tools / APIs:
  - MetPred (Uppsala University)
  - FAME3 (UHH/HITeC Hamburg; implementation challenge)
  - enviPath, UM-PPS (JGU Mainz)
  - SMARTCyp (external service, integrated by VU Amsterdam)
  - Plasticity tools (VU Amsterdam)
- **Jupyter Notebooks to collect and visualize results**

MetPred

Predicts phase I metabolites: MetPred ranks most probable sites-of-metabolism (SOMs) and reaction types based on similar atom environments and ReactionSMARTS in annotated dataset [webservice; API available]





Carlsson et al. BMC Bioinformatics 2010
Arvidsson et al. Proc. Machine Learn. Res. 2017

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Risk Assessment Framework
Tier 0.1 (mol. structure), 1.5 (biokinetics), 1.6 (MoA)

AIM: Integration of tools for site-of-metabolism (SOM) and metabolite prediction

Ligand-based metabolite predictors (e.g. MetPred, FAME, SMARTCyp) and incorporate protein-structure and -dynamics based approaches to predict the site of metabolism (SOM) by Cytochrome P450 (CYPs), which metabolize ~75% of the currently marketed drugs.

Objectives: Integration, comparison and combination of tools for metabolism prediction

- Ligand-based Site-Of-Metabolism (SOM) prediction using reaction SMARTS, circular fingerprints and/or atomic reactivities
- QSBR (quantitative-structure biotransformation relationship) modeling of microbial biotransformation
- Protein-structure and -dynamics based prediction of CYP450 isoform specific binding and SOMs
- Predicting probabilities for specific reaction type events

Databases For the purpose of method development and model calibration and/or verification, data from XMetDB and other open-access databases for drugs, xenobiotics and their respective metabolites can be used

XMetDB, SMARTcyp, ZINC, ChEMBL, EAWAG-BBD

Tools / APIs

- MetPred (UU)
- FAME3 (UHH/HITeC; implementation challenge)
- enviPath, UM-PPS (JGU)
- SMARTCyp (external service, integrated by VU)
- Plasticity tools (VU)

Service integration

To facilitate combining metabolite prediction approaches or using MetaP outcomes as input for other predictors, we take advantage of available workflow management systems and we have explored integration of Jupyter Notebooks into the platform. This aids in investigating the added value of having multiple predictors available, which has been subject of a pilot study on metabolite prediction.