Application of BioPath Metabolism Tools within ChemTunes·ToxGPS for Next Generation Risk Assessment

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Motivation

- **ChemTunes·ToxGPS** is a comprehensive platform for Next Generation Risk Assessment (NGRA)
- It includes databases and computational tools and workflows addressing chemical, toxicological and biological domains for analysis of target compounds and analog candidates
- Unique combination of toxicity data and information about metabolic transformations
- We present case study of caffeine to demonstrate how metabolism-related components of the system can be used to facilitate the selection of high-quality analogs and increase the reliability of final WOE outcome.

Metabolism Database Content

Exogenous pathways for xenobiotics:

- Hepatic (mostly human) transformations for drugs, up to five levels of metabolic degradation
- In vitro/in vivo studies in laboratory rodents, primates, and farm animals for pesticides.
- 500 parent substances, >5000 metabolites and 3000 phase I and II reactions (>140 reaction types)
- Classification into major and minor metabolites

Endogenous pathways:

- Metabolic transformations and cellular regulations from Roche "Biochemical Pathways" wall chart and literature data
- Information on enzymes (name and EC) and pathways (names)
- Prokaryotes, animals, plants, yeast and general pathways
- >14,500 chemical structures, >3,900 chemical reactions, 640 pathways

ChemTunes Metabolizer

- Rule-based system for generation of metabolites
- Human hepatic transformations
- Over 140 reaction types: phase I functionalization reactions mediated by P450 isoforms (cleavage, hydrolysis, hydroxylation, lactam/lactone formation, oxidation, rearrangement, reduction) and phase II conjugations (acylation, glucuronidation, glycination, methylation, phosphorylation, sulfation)
- Metabolites ranked and filtered according to estimated likelihood of occurrence (ppv and odds ratios) derived from a database of metabolic reactions and further refined using our pristine in vitro human hepatocyte data

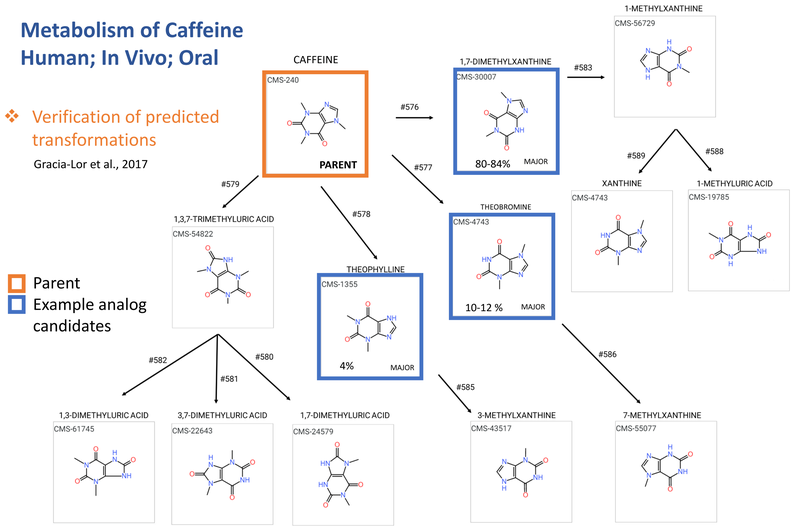
ChemTunes Metabolism Database

Metabolism of Caffeine
Human; In Vivo; Oral

- Verification of predicted transformations

Gracia-Lor et al., 2017

Parent
Example analog candidates



Analog Quality Assessment

Compound Information		1	3	4	5
Summary					
Identifiers	CMS ID	CMS-240	CMS-1355	CMS-4743	CMS-30007
	Name	CAFFEINE	THEOPHYLLINE	THEOBROMINE	1,7-DIMETHYLXANTHINE
Analog Quality		1	0.76	0.83	0.9
Chemical Similarity Tanimoto	**1.**				
	RDKit Mol		0.92	0.92	0.90
	RDKit MACCS		0.96	0.96	0.96
	RDKit Morgan		0.50	0.56	0.56
	ToxPrint		0.93	0.87	1.00
	Liver BioPath		0.71	0.71	1.00
	Skin Metabolism Substrates		0.50	1.00	1.00
Dice					
	RDKit Mol		0.96	0.96	0.95
	RDKit MACCS		0.98	0.98	0.98
	RDKit Morgan		0.67	0.72	0.72
	ToxPrint		0.96	0.93	1.00
	Liver BioPath		0.83	0.83	1.00
	Skin Metabolism Substrates		0.67	1.00	1.00
Cosine					
	RDKit Mol		0.96	0.96	0.95
	RDKit MACCS		0.98	0.98	0.98
	RDKit Morgan		0.67	0.72	0.72
	ToxPrint		0.96	0.93	1.00
	Liver BioPath		0.83	0.83	1.00
	Skin Metabolism Substrates		0.71	1.00	1.00
Chemotype Profiles	**2.**				
Liver BioPath Rules (# hits)		10	10	9	9
Skin BioPath Rules (# hits)		2	2	2	2
Skyline Plots skyline - properties	**3.**				
	Skyline				
	Pearson similarity (0-1)		0.99	0.99	0.99
	Euclidean similarity		0.90	0.91	0.90
TOX21CAST					
Xenobiotic Metabolism / P450 (32)	**4.**				
	Skyline				
	Pearson similarity (0-1)		0.62	0.65	NA

- Custom selection of metrics to be considered for calculation of Analog Quality (AQ)
- AQ is a geometric mean of all selected similarity measures

1. Chemical Similarity

- Structure based similarity
- Metabolic similarity in liver and skin

2. Metabolic Profilers

- Liver: >140 csrml rules to detect and mark reaction centers (atoms, bonds, and substructures) in a molecule which can undergo human hepatic phase I and II metabolic transformations
- Skin: 80 csrml rules specific for dermal transformations catalyzed by skin enzymes: oxidoreductases, transferases (e.g., conjugation reactions), hydrolases, lyases, and isomerases

3. Property-based Similarity

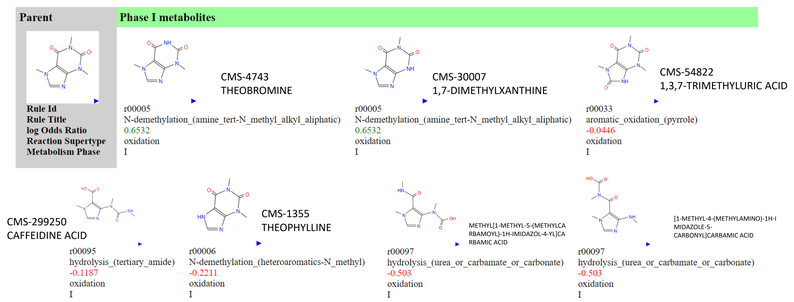
- Skyline plots include: #Atoms, #RotBonds, H-Acceptors & Donors, #Rule-of-Five Violations, Stereocenters, MW, Complexity, TPSA, LogP, HoF, HOMO, LUMO, HOMO/LUMO gap

4. Biological Activity

- Tox21/Cast Assay Vectors

PREDICTED METABOLISM OF CAFFEINE

1st level of metabolism



Conclusions

- We present how various components of ChemTunes.ToxGPS can be used to select high-quality analogs accounting for various types of similarity, increase the reliability of final RA outcome & support NGRA

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