Reaction Representation and Structure Transformation with Ambit-SMIRKS. Application in Metabolite Prediction

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Ambit-SMIRKS is a new extension of the **Ambit-SMARTS** Java library [1], both part of the Ambit2 [2] project. Implemented on top of Chemistry Development Kit [3], the SMIRKS module is used to enable metabolite predictions in **Toxtree** [4], once that site of metabolisms are predicted by **SMARTCyp** [5].

Ambit-SMIRKS main tasks:

(1) Parsing of SMIRKS linear notations into internal reaction (transformation) representations based on CDK objects

(2) Application of the stored reactions against target molecules for actual transformation of the target chemical objects

Ambit-SMARTS basic features:

(1) Effective representation of SMARTS Queries based on CDK (full Daylight syntax)

(2) Fast structure isomorphism /mapping/

(3) Support of recursive SMARTS

(4) Syntax extensions

SMIRKS Parsing

Input SMIRKS:
[N:1]1[C:2][C:3]=[C:4][C:5]1>>[N:1]1[C:2]=[C:3][C:4]=[C:5]1

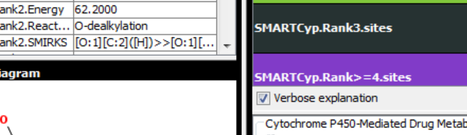
Parse SMIRKS components

[N:1]1[C:2][C:3]=[C:4][C:5]1 [N:1]1[C:2]=[C:3][C:4]=[C:5]1

Parse Reactant SMARTS → CDK object

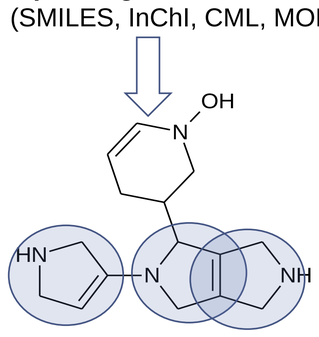
Parse Mapping

Parse Product SMARTS → CDK object

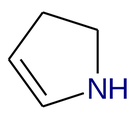


SMARTS searching

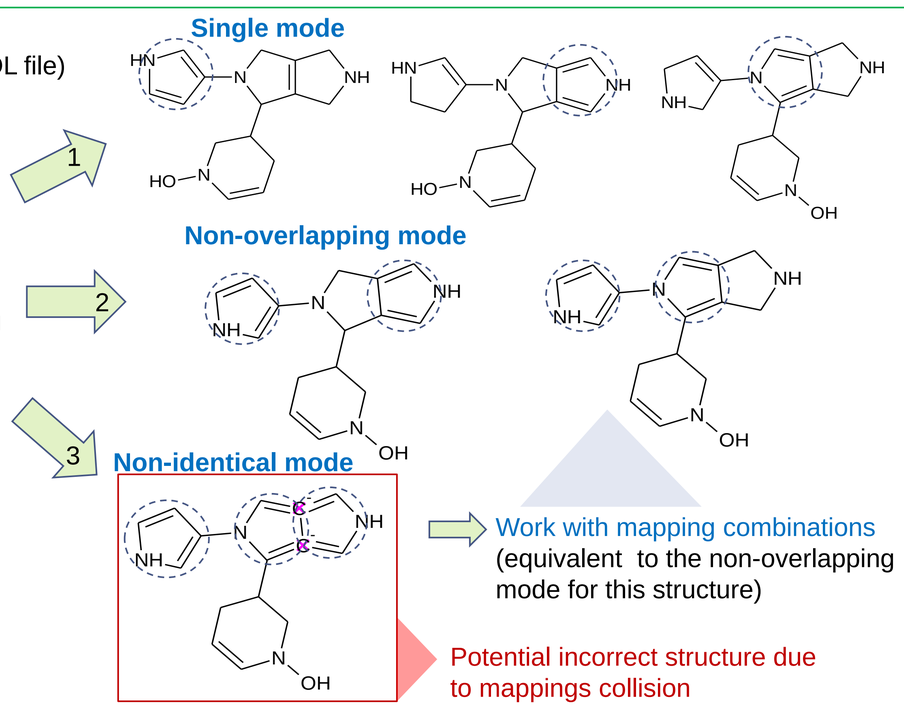
Input Target Molecule
(SMILES, InChI, CML, MOL file)



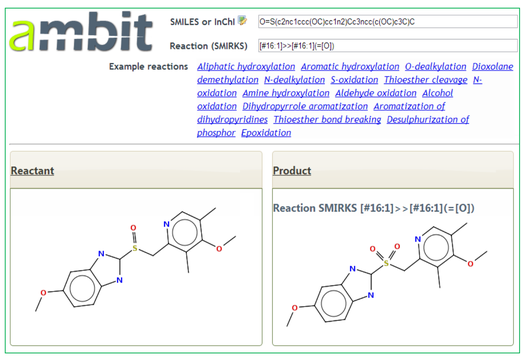
Reactant fragment found at 3 positions



Transformation application



http://tinyurl.com/testreaction



Transformation mapping modes

The transformations can be applied on various sites of the target molecule in several modes:

(1) single
(2) non-overlapping,
(3) non-identical,
(4) non-homomorphic or
(5) externally specified list of sites.

SMIRKS Application in metabolite generation

(1) Toxtree is an open-source application that predicts various kinds of toxic effects, mostly by applying structural alerts, arranged in a decision tree fashion **http://toxtree.sourceforge.net/predict/**

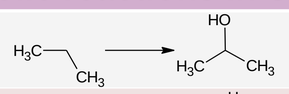
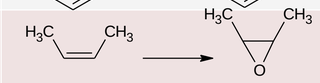
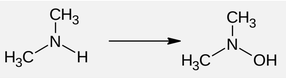
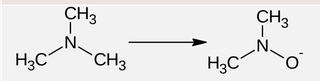
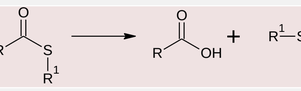
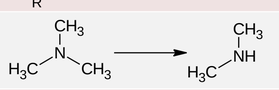
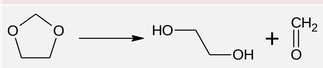
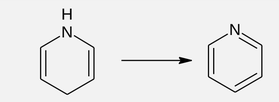
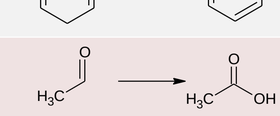
(2) SMARTCyp (Cytochrome P450-Mediated Drug Metabolism) model is developed by Patrik Rydberg et al [5] and is included as Toxtree module since Toxtree 2.1.0.

Application of Ambit-SMIRKS module for prediction of **Omeprazole** metabolism

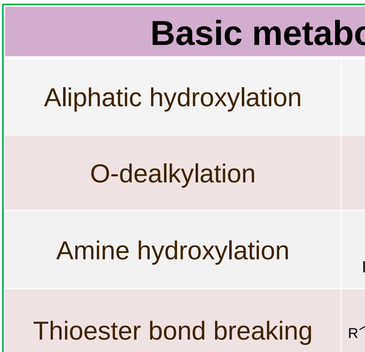
Sites of metabolism as predicted by **SMARTCyp**

Ambit-SMIRKS generated metabolites

Basic metabolic reactions in SMARTCyp implemented by Toxtree

Aliphatic hydroxylation		Aromatic hydroxylation	
O-dealkylation		Epoxidation	
Amine hydroxylation		N-oxidation	
Thioester bond breaking		Alcohol oxidation	
N-dealkylation		Dioxolane demethylenation	
S-oxidation		S-oxidation	
Aromatization of dihydropyridines		Dihydropyrrole aromatization	
Aldehyde oxidation		Desulphurization of phosphor	

Importance of metabolism prediction



Virtual safety testing (Ames models)

		Model 1	Model 2	Model 3
1	**Clozapine**	0	1	0
2	Norclozapine	0	1	0
3	Clozapine N-oxide	1	1	0
4	Hydroxyclozapine	0	1	0

Toxic metabolites are formed in some cases leading to unwanted adverse effects. Safety testing of metabolites has become a requirement according to the guidance for industry issued by regulatory institutions.

References:

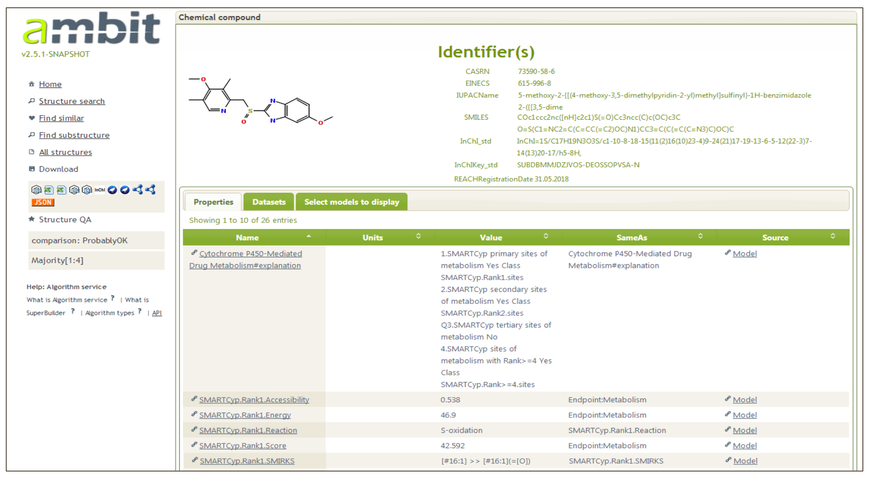
[1] N. Jeliazkova, N. Kochev, AMBIT-SMARTS: Efficient Searching of Chemical Structures and Fragments, Mol. Inf., 30: 707–720, 2011

[2] Jeliazkova N., Jeliazkov V. AMBIT RESTful web services: an implementation of the OpenTox application programming interface, Journal of Cheminformatics 2011, 3:18, doi:10.1186/1758-2946-3-18.

[3] C. Steinbeck, Y. Han, S. Kuhn, O. Horlacher, E. Luttmann, E. Willighagen, The Chemistry Development Kit (CDK): An Open-Source Java Library for Chemo- and Bioinformatics, J. Chem. Inf. Comput. Sci., 43: 493–500, 2003

[4] http://toxtree.sourceforge.net

[5] P. Rydberg, D. Gloriam, J. Zaretzki, C. Breneman, L. Olsen, SMARTCyp: A 2D Method for Prediction of Cytochrome P450-Mediated Drug Metabolism, ACS Med. Chem. Lett., 2010, 1 (3), pp 96-100



Predictions via AMBIT web services (OpenTox API)

http://ambit.sf.net