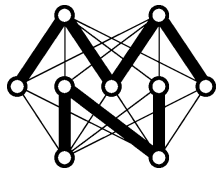

Molecular Networks
Inspiring Chemical Discovery

Risk Assessment of Chemicals and Prediction of Metabolism

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Molecular Networks GmbH
Henkestraße 91
91052 Erlangen, Germany
www.molecular-networks.com

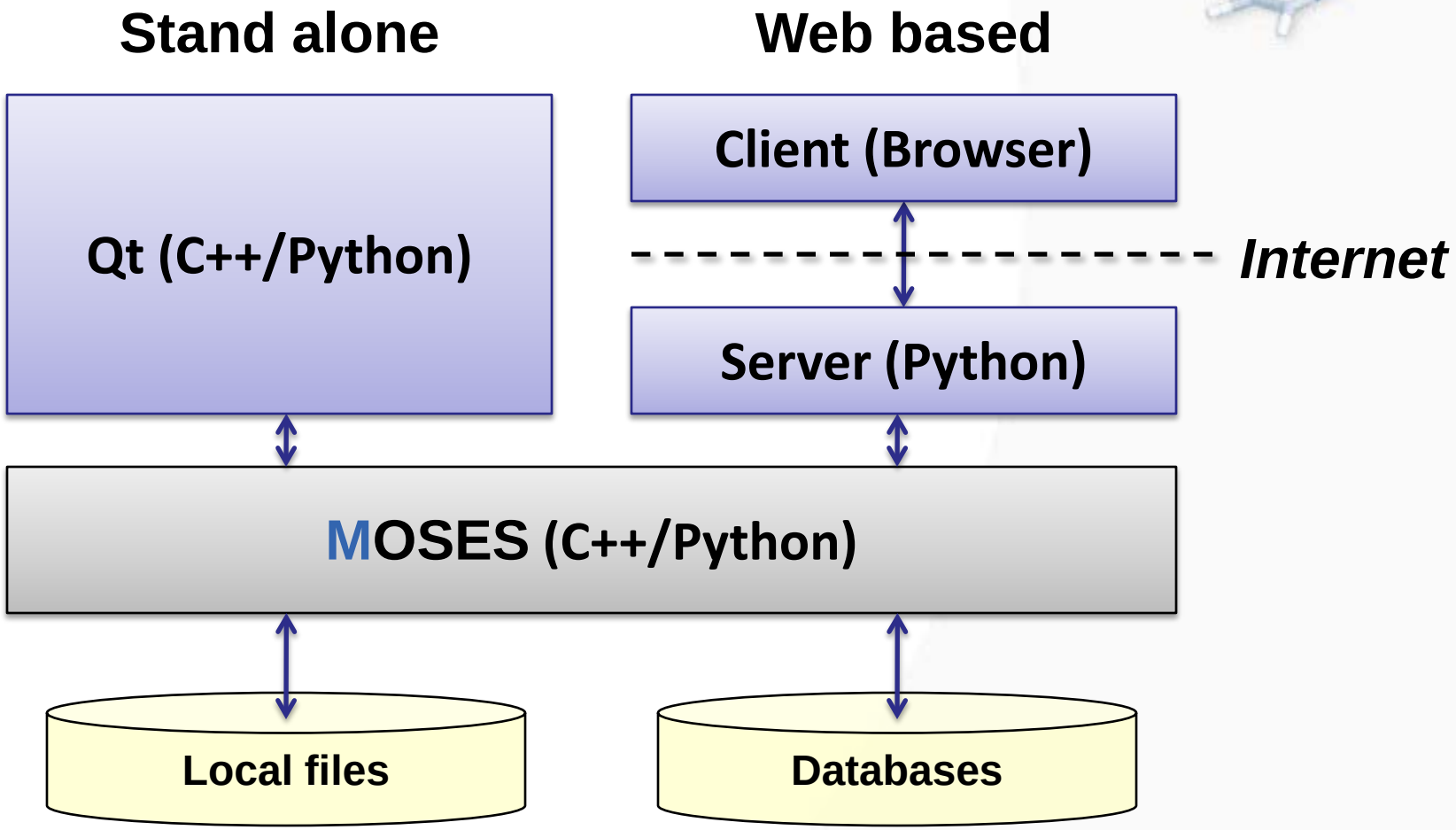
Outline

- MOSES system
- Structure representation
- Toxicity prediction
- MOSES.ChemistryToolbox
- Metabolism of xenobiotics
- MOSES.Metabolism
- MOSES.RiskAssessment

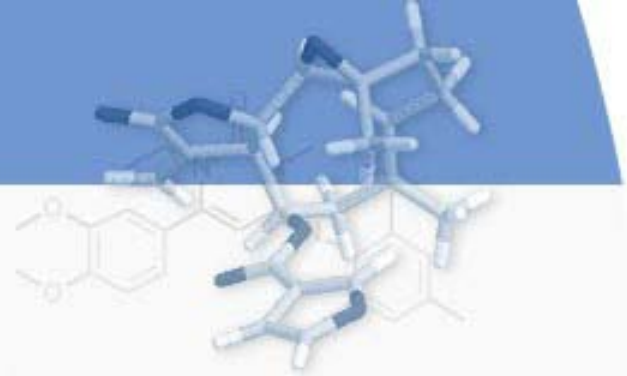
MOlecular Structure Encoding System

- **C++ based Chemoinformatics toolkit**
  - ***high performance***
  - ***available for many platforms (Windows, Linux, Unix)***
- **Python interface available**
  - ***provides easy access to the full functionality of MOSES***
  - ***ideally suited for the development of client / server solutions***
- **under active development since 2001**
  - ***Computer-Chemie-Centrum, Universität Erlangen-Nürnberg***
  - ***Molecular Networks GmbH***
- **300,000 lines of code**
  - ***well documented and tested***

User Interfaces



Modeling Chemical Structures and Reactions



- **Theoretical chemist:**
  - ***Quantum-mechanical* calculations: time-consuming**

- **Organic chemist:**
  - ***Concepts* for rationalizing chemical reactivity and reaction mechanisms**
  - ***Partial charges, inductive, resonance, polarizability, steric effect***

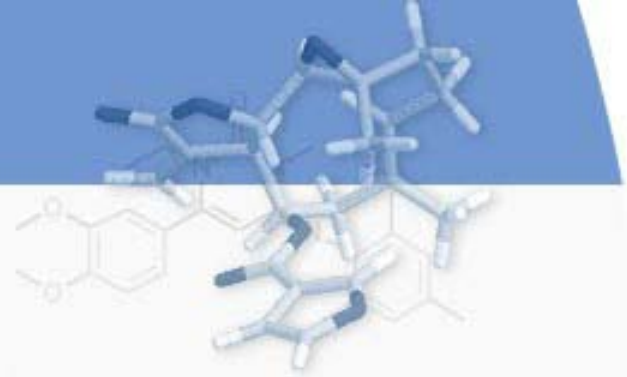
→ **Quantify these physicochemical effects**

Calculation of Physicochemical Effects

- Charge calculation: q_σ and q_π
- Inductive effect: χ_r
- Resonance effect: M^+, M^-
- Polarizability effect: α_d
- Steric accessibility: A_{access}
- Heats of formation/heats of reaction

PETRA package

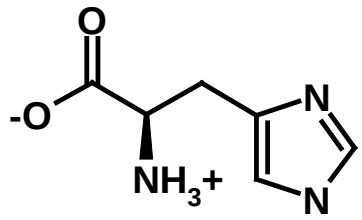
(Parameter Estimation for the Treatment of Reactivity Applications)



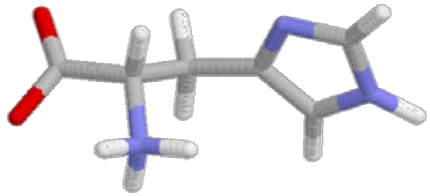
Representation of chemical structures

Hierarchy of interpretable structure descriptors

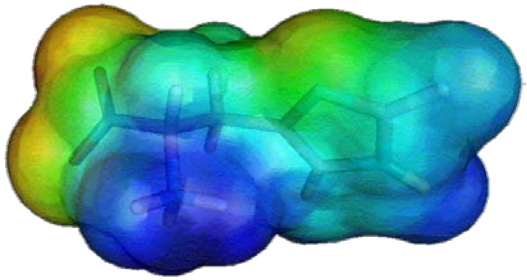
Structure Representation



- **Constitution**



- **3D model**

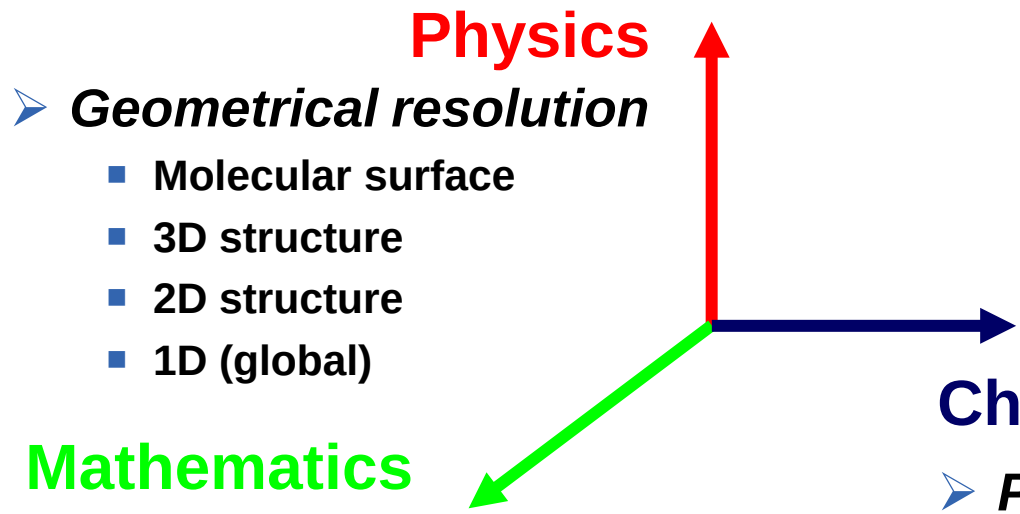


- **Molecular surface**

J. Gasteiger, *Of Humans and Molecules*,
J. Med. Chem., **2006,** *55,* 6429 - 6434

ADRIANA.*Code* – Covered Descriptor Space

- **Structure coding spanned by 3 axes in descriptor space**



- ***Geometrical resolution***
  - Molecular surface
  - 3D structure
  - 2D structure
  - 1D (global)

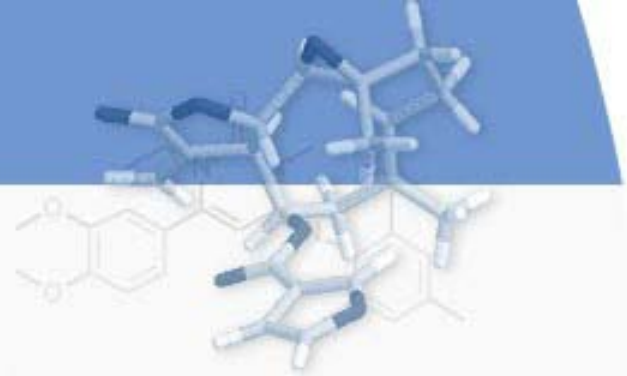
Mathematics

- ***Mathematical transformation***
  - 2D autocorrelation
  - 3D autocorrelation
  - Radial distribution functions
  - Autocorrelation of surface points

Chemistry

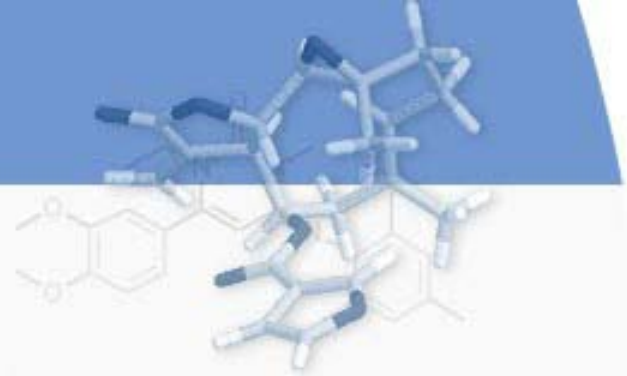
- ***Physicochemical properties***
  - Global properties
  - Atomic properties: charges, polarizabilities, electronegativities
  - MEP, HBP, HPP

ADRIANA.*Code* – Areas of Application



- **Drug design**
  - ***Clustering of compounds according to their biological activity***
  - ***Locating biologically active compounds in sets of diverse chemical compounds***
  - ***Quantitative prediction of biological activities***
  - ***Analysis of results of high-throughput screening***
- **Prediction of ADME/Tox properties**
  - ***Aqueous solubility of organic compounds***
  - ***pKa values***
  - ***Prediction of major metabolizing CYP450 isoform***
  - ***Classification of toxic mode of action***
- **Prediction of infrared and ^{1}H NMR spectra**
- **Dye design**

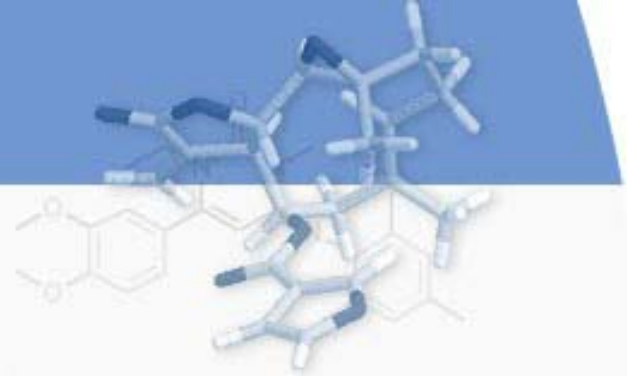
For list of publications:
http://www2.chemie.uni-erlangen.de/publications/



Modeling toxicity of compounds

Combination of descriptors

Modeling of Toxicity

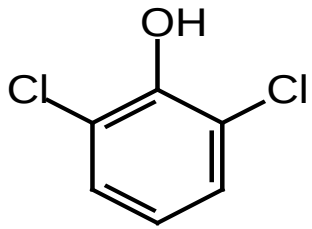


- **Different data analysis methods**
  - S.Spycher, M.Nendza, J.Gasteiger, *QSAR Comb. Sci.,* **2004***, 23,* 779-791
- **Representation of chemical structures**
  - S.Spycher, E.Pellegrini, J.Gasteiger*, J.Chem.Inf.Model*., ***2005***, 45, *200-208*
- **Considering toxicological mechanism**
  - S.Spycher, B.Escher, J.Gasteiger, *Chem.Res.Toxicol.,* **2005***,18,* 1857-1867

Why Prediction of Toxic Mode of Action (MOA)?

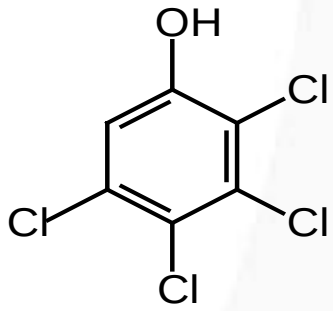
Most QSARs in toxicology focus on a certain class of compounds

However:



polar narcotic

and

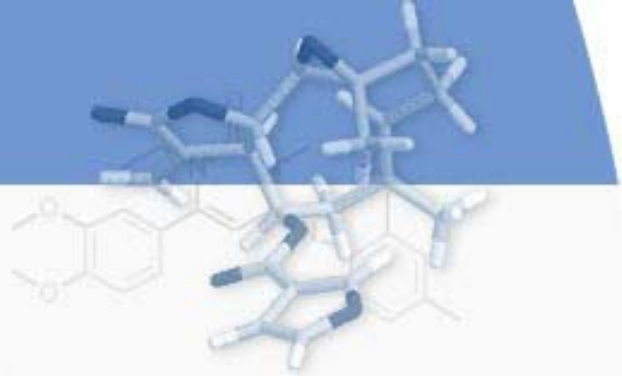


uncoupler of oxidative phosphorylation

Require different QSAR-equations

→ **First classify structures according to their MOA**

Dataset: MOA of Phenols



1. **Polar narcotics**	**(156 cpds)**
2. **Uncouplers of oxidative phosphorylation**	**(19 cpds)**
3. **Precursors to soft electrophiles**	**(24 cpds)**
4. **Soft electrophiles**	**(22 cpds)**
	221 cpds

Dataset:

A.O.Aytula, T.I.Netzeva, I.V.Valkova, M.T.D.Cronin, T.W.D.Schultz, R.Kühne, G.Schüürmann, *Quant. Struct.-Act. Relat*. **2002**, *21*, 12-22.

Study:

S.Spycher, E.Pellegrini, J.Gasteiger, *J. Chem. Inf. Model.,***2005,** *45*, 200-208

Predictive Power of Model (Counterpropagation-Neural Network)

estimate of predictive power with 5-fold cross-validation:

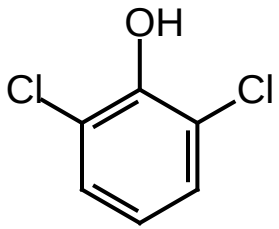
RDF(χ_{LP}, χ_{σ}), HBP surface AC 95.9%

(2×8 + 12) descriptors

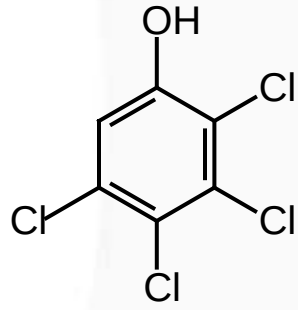
RDF: radial distribution function
HBP: hydrogen bonding potential

S.Spycher, E.Pellegrini, J.Gasteiger, *J. Chem. Inf. Model.,* **2005,** *45*, 200-208

Classification in 5-fold Crossvalidation



polar narcotic



uncoupler of oxidative phosphorylation

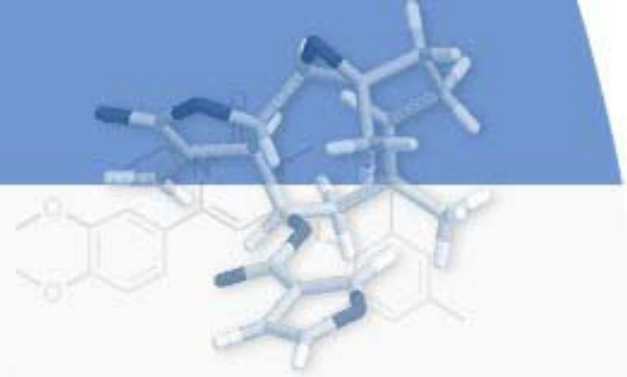
Correct classification !

Molecular Networks
Inspiring Chemical Discovery

MOSES.ChemistryToolbox

Molecular Networks GmbH
Henkestraße 91
91052 Erlangen, Germany
www.molecular-networks.com

MOSES.ChemistryToolbox

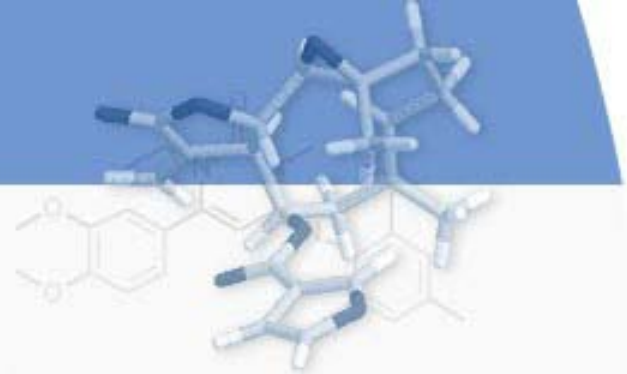


- **Program package for the prediction of physical, chemical or biological properties of compounds**
- **Representation of chemical structures for QSAR studies**
- **Combining the descriptor calculation of ADRIANA.Code with structural features**

MOSES.ChemistryToolbox – Structural Features

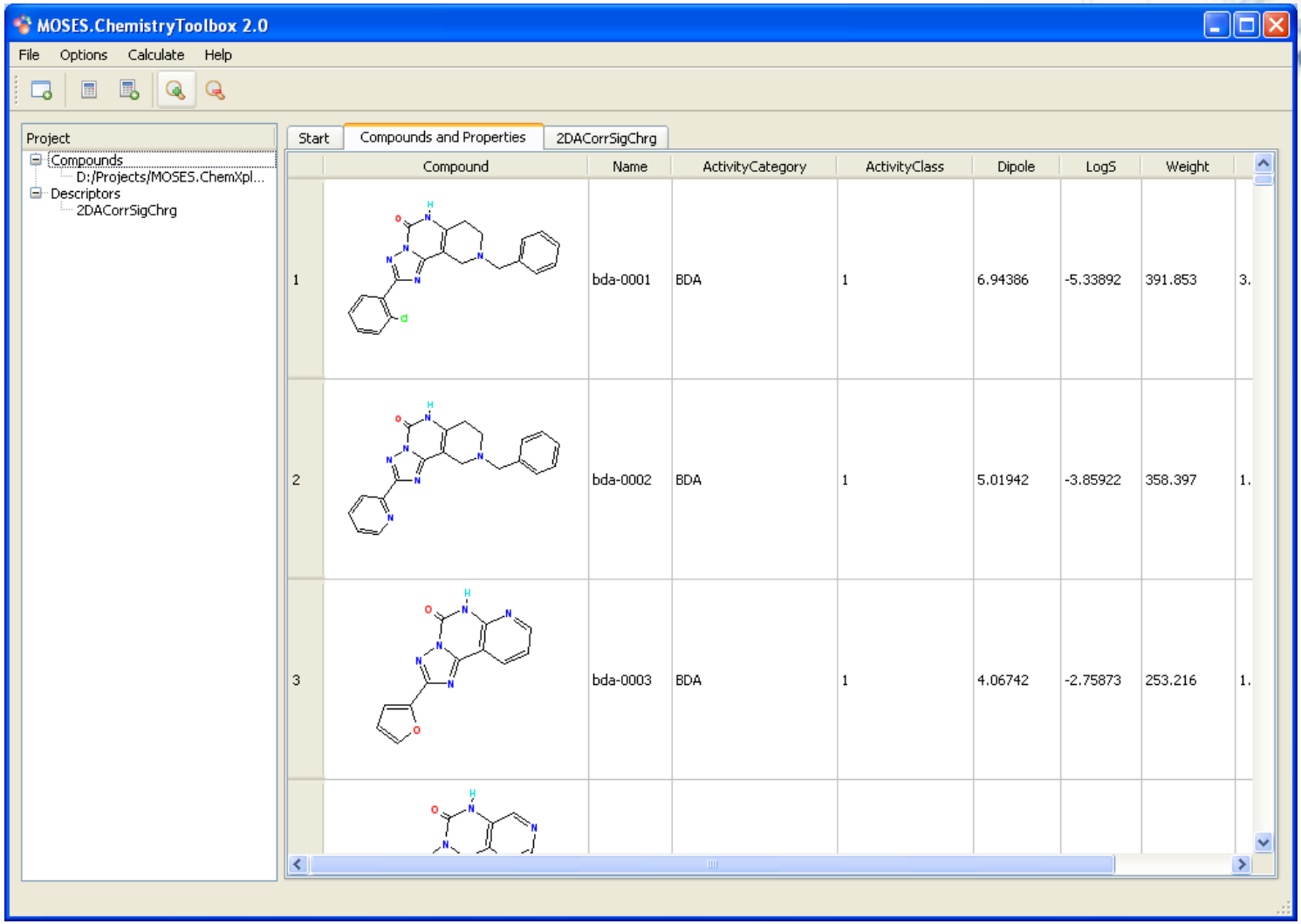
- **Functional groups, e.g.:**
  - ***aldehyde, aromatic***
  - ***aldehyde, alkenyl***
  - ***aldehyde, alkyl***
  - ***amine, tert-N, alkyl***
  - ***amine, sec-NH, aromatic***
  - ***amine, aromatic, N-hydroxy***
  - ***halide, prim-alkyl***
  - ***silane, trimethyl***
  - ***Michael acceptor***
  - ***urethane derivative***
- **Structural elements, e.g.:**
  - ***benzofuran***
  - ***imidazole***
  - ***quinoxaline***
  - ***pyrrolidine***
  - ***purine***
  - ***guanidine***
  - ***steroid***
  - ***pyrazine***
  - ***aflatoxin***
  - ***pyrimidine***

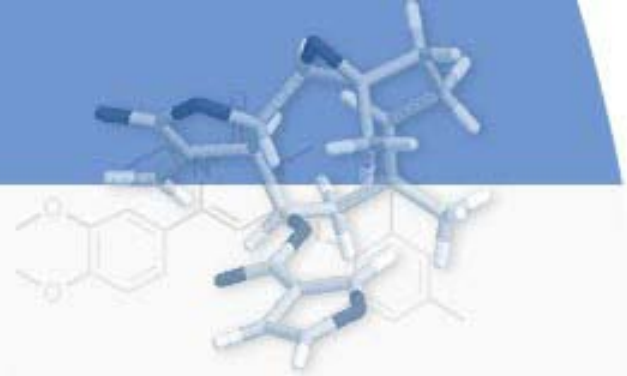
MOSES.ChemistryToolbox - Functionalities



- Reading of chemical structure files (SDFiles, SMILES, etc.)
- Merging of multiple files into one spreadsheet
- Calculation of physicochemical properties
- Calculation of structural class fingerprints
- Browsing of structures and properties as spreadsheet with database backend
- Output of spreadsheet as structure files
- Output of spreadsheet as table file (compatible with Excel)
- Project management

MOSES.ChemistryToolbox





Classification model for salmonella reverse mutation

Study performed by Dr. Chihae Yang, FDA CFSAN

Modeling process: OECD-compliant

- Training set (salmonella reverse mutation)
  - Transparency
  - biological and chemicals modes of activities
- Interpretable descriptors
  - Structural features
  - Calculated molecular properties
- Statistical algorithms and inference
  - fitting/parameter optimization/cross-validation
- External validation

Descriptors: Structural Features

- FDA Redbook inspired features
  - Generic compound class features
  - Classes defined in Cramer classes
  - Categories for Threshold of toxicological concern
- Known alerts
  - Ashby Tennant genotoxic carcinogen alerts
- Alerts learned from the dataset

ADRIANA.CODE Descriptors

- Whole molecule descriptors
  - xLogP, topological polar surface area, water solubility, molecular weight, (heavy) atom count, hydrogen bond acceptors and donors (N and O specific), Lipinski score violation, rotational bonds, ring complexity
- Electrostatic properties
  - charges (sigma, pi, and lone pair)
  - electronegativity (sigma, pi, and lone pair)
- Surface properties.
- Molecular shape

Performance Comparisons

Model Name	Pos/Neg	Descriptor	PLS factor	Sensitivity	Specificity
Aromatic Amines	321/417	Structure	3	78	62
		ADRIANA	3	82	50
		Both	4	78	89
Halides	379/530	Structure	2	77	82
		ADRIANA	8	64	81
		Both	4	77	88
Global	1807/2490	Structure	10	64	87
		ADRIANA	30	54	85
		Both	19	78	88
Phenols	283/370	Structure	3	66	88
		ADRIANA	10	68	81
		Both	8	84	93

Performance Comparisons

Model Name	Pos/Neg	Descriptor	PLS factor	Sensitivity	Specificity
Aldehydes	58/34	Structure	4	74	81
		ADRIANA	5	67	78
		Both	2	97	94
Halides, aliphatic	181/247	Structure	3	81	68
		ADRIANA	7	85	62
		Both	4	80	91
Azo-Azoxy	64/34	Structure	5	76	62
		ADRIANA	2	82	46
		Both	2	95	94
Hydrazine	62/34	Structure	2	80	81
		ADRIANA	9	86	77
		Both	2	97	94

Summary

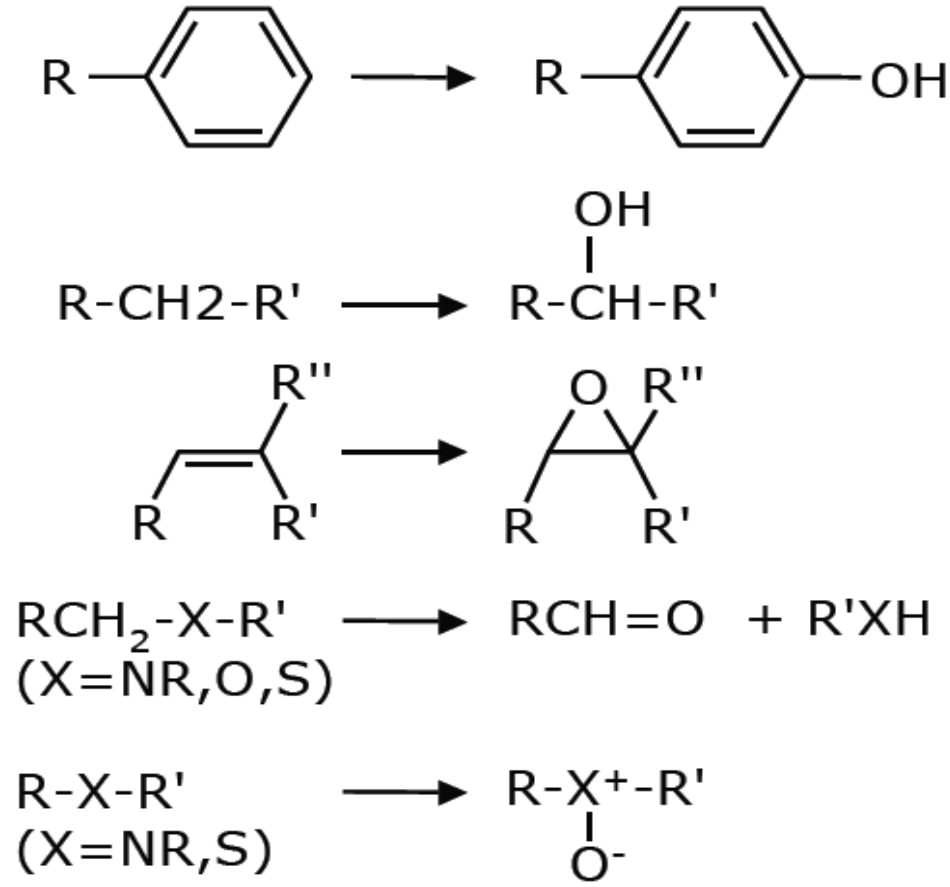
- Both structural features and physicochemical descriptors (ADRIANA.Code) perform equally good
- However, they catch different information
- Therefore, the combined use of structural features and physicochemical descriptors leads to markedly improved models and predictions

Metabolism of xenobiotics

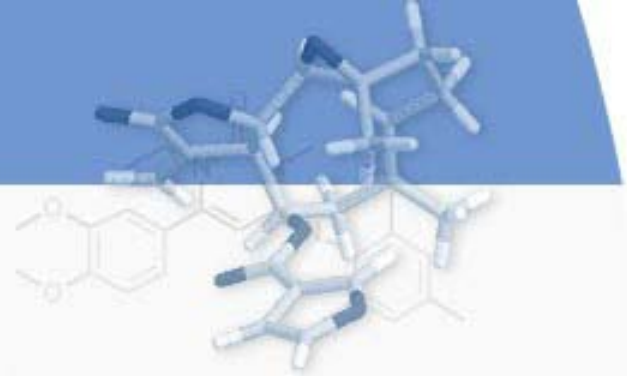
Drugs, agrochemicals, food additives

Oxidations by Cytochrome P450

- **Aromatic hydroxylation**
- **Aliphatic hydroxylation**
- **Epoxidation**
- **N, O, S-dealkylation, oxidative deamination**
- **N,S-oxidation**

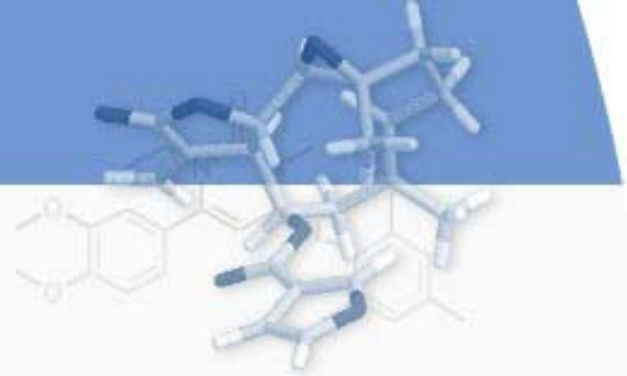


Different Selectivities



- **Selectivity between different cytochrome P450 isoenzymes**
  - ***3A4, 2C9, 2C19, 2D6, 1A2***
- **Selectivity between different reaction types**
  - ***chemoselectivity***
- **Selectivity between different reaction sites**
  - ***regioselectivity***

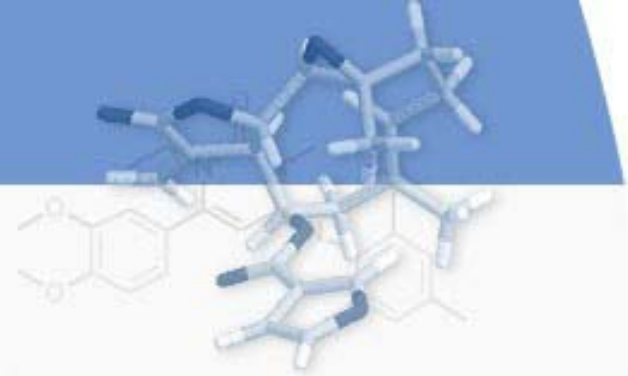
Data Set of 3A4, 2D6, and 2C9 Substrates



- **Training and test data set: 146 compounds**
  - ***Manga et al, SAR and QSAR in Environm. Res. 2005, 16, 43-61***
  - ***80 3A4 substrates (55%)***
  - ***45 2D6 substrates (31%)***
  - ***21 2C9 substrates (14%)***

- **Validation data set: 233 compounds**
  - ***Metabolite database***
  - ***144 3A4 substrates (62%)***
  - ***69 2D6 substrate (30%)***
  - ***20 2C9 substrates (8%)***

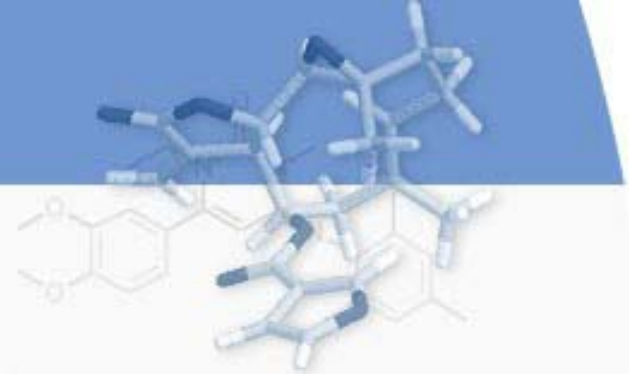
Support Vector Machine (SVM) Model



- **Descriptors (242 components)**
- **Automatic variable selection: 12 components**
  - *2D-AC$_{identity}$(5), 2D-AC$_{q\pi}$(3), 2D-AC$_{q\pi}$(6), 2D-AC$_{\chi\pi}$(5), 2D-AC$_{q\sigma}$(1), 2D-AC$_{q\sigma}$(2), 2D-AC$_{\chi\sigma}$(6), 3D-AC$_{identity}$([5.8-5.9[Å), n$_{acid_groups}$, n$_{aliphatic_amino}$, n$_{basic_n}$, r$_3$*

	Predictability
Training:	**90.4%**
5-fold CV:	**87.8%**

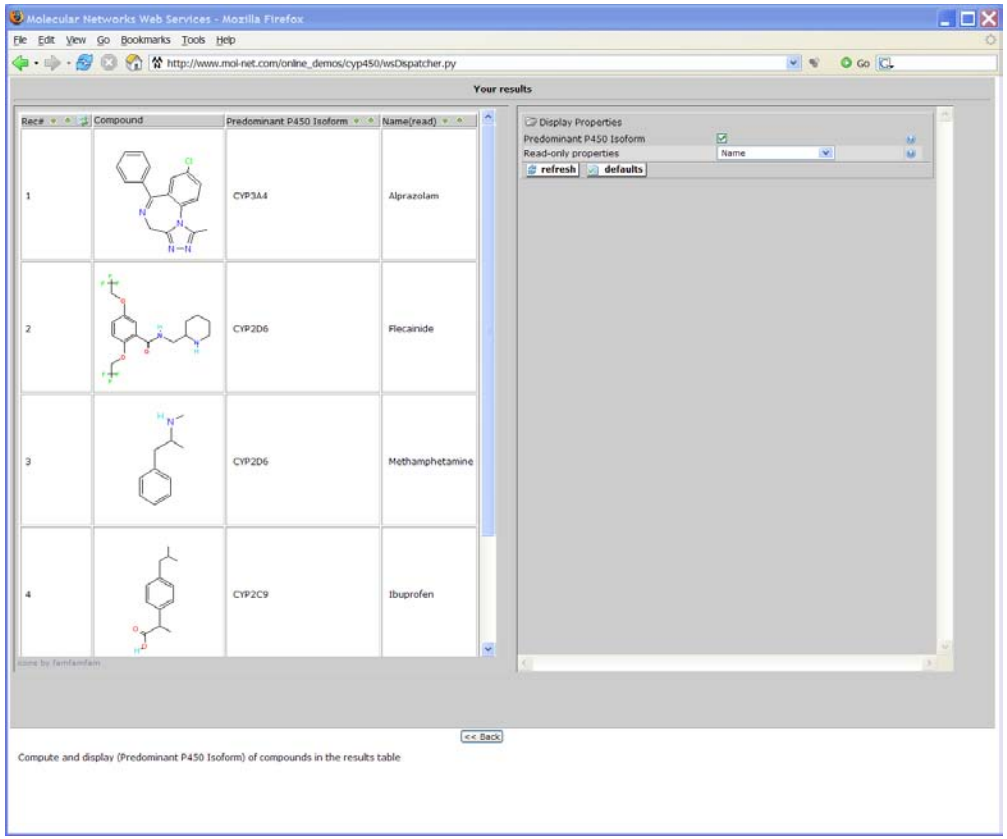
Validation of the Support Vector Machine Model



- **Validation set: 233 substrates from the Metabolite database**
- **Predictability: 82.8%**
- **remember: some drugs are metabolized by several isoforms**

L. Terfloth, B. Bienfait, J. Gasteiger, *J. Chem. Inf. Model.* **2007,** *47,* 1688-1710

isoCYP Webservice

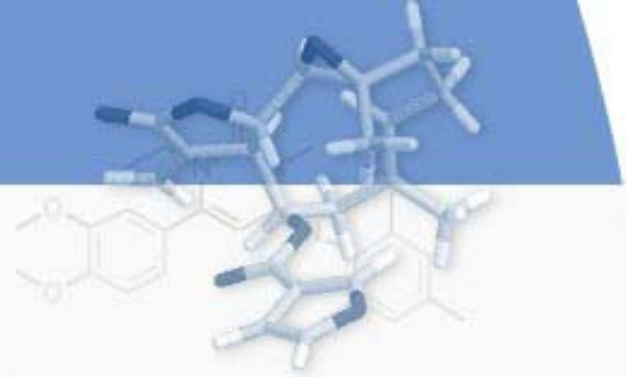


Prediction of major metabolizing CYP450 isoform (2D6, 3A4, 2C9)

- **http://www.molecular-networks.com/online_services**

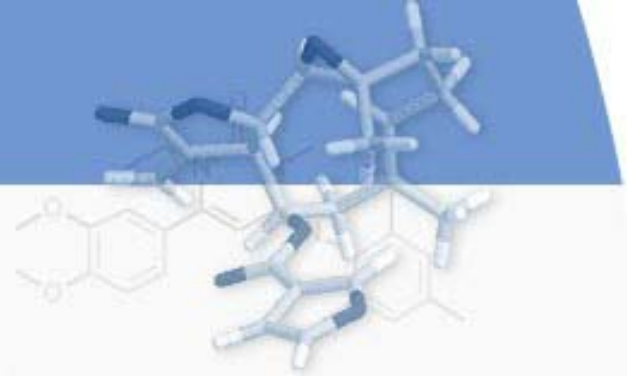
L. Terfloth, B. Bienfait, J. Gasteiger, *J. Chem. Inf. Model.* **2007,** *47,* 1688-1710

Different Selectivities



- **Selectivity between different cytochrome P450 isoenzymes**
  - ***in particular 3A4, 2C9, 2C19, 2D6, 1A2***
- **Selectivity between different reaction types**
  - ***chemoselectivity***
- **Selectivity between different reaction sites**
  - ***regioselectivity***

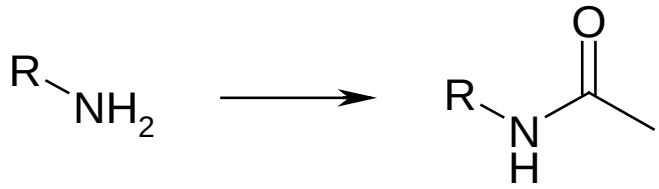
MOSES.Metabolism Reaction Rules



- **117 reaction rules**
- **Reaction types covered:**
  - ***Aromatic hydroxylation***
  - ***Aliphatic hydroxylation***
  - ***N- and O-dealkylation***
  - ***Hydrolysis (ester, amides)***
  - ***Conjugation reactions (glucuronidation, sulphation, glycination, acetylation)***
  - ***Oxidation reactions (alcohols, aldehydes, etc.)***
- **Empirical score for probability of a reaction based on literature data**

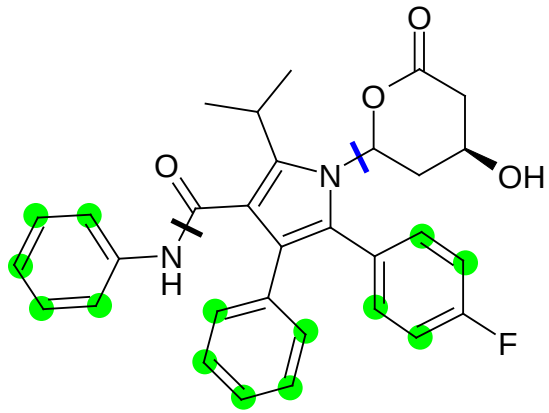
Derivation of a Rule Base for Metabolite Prediction

- **Define reaction rules, e.g. for an acetylation**



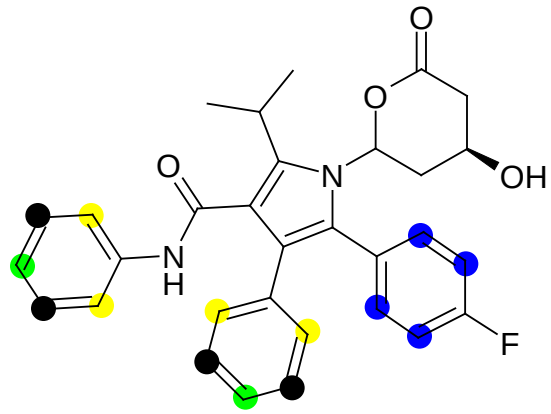
- **Calculate reaction probabilities based on a reaction database (Metabolite, MDL-Symyx)**
  - ***Conceivable metabolites*** ***1223***
  - ***Observed metabolites*** ***122***
  - ***Non-observed metabolites*** ***1101***
  - ***Probability*** ***122/1223 = 0.10***

Phase I Metabolism of Atorvastatin Lactone



- **Chemoselectivity**
  - ***Aromatic hydroxylation (●)***
  - ***Amide hydrolysis (\)***
  - ***N-Dealkylation (\ )***

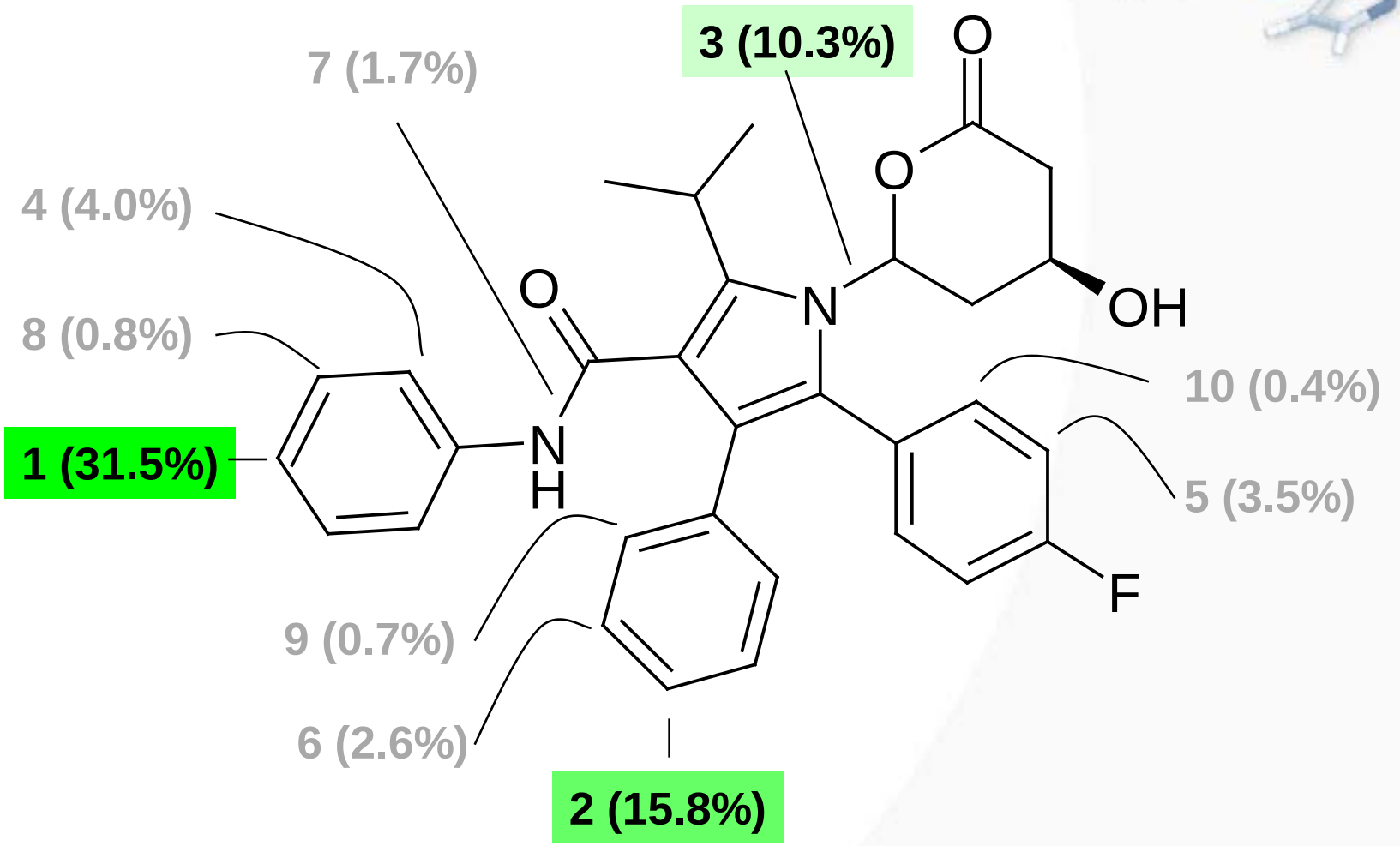
Phase I Metabolism of Atorvastatin Lactone



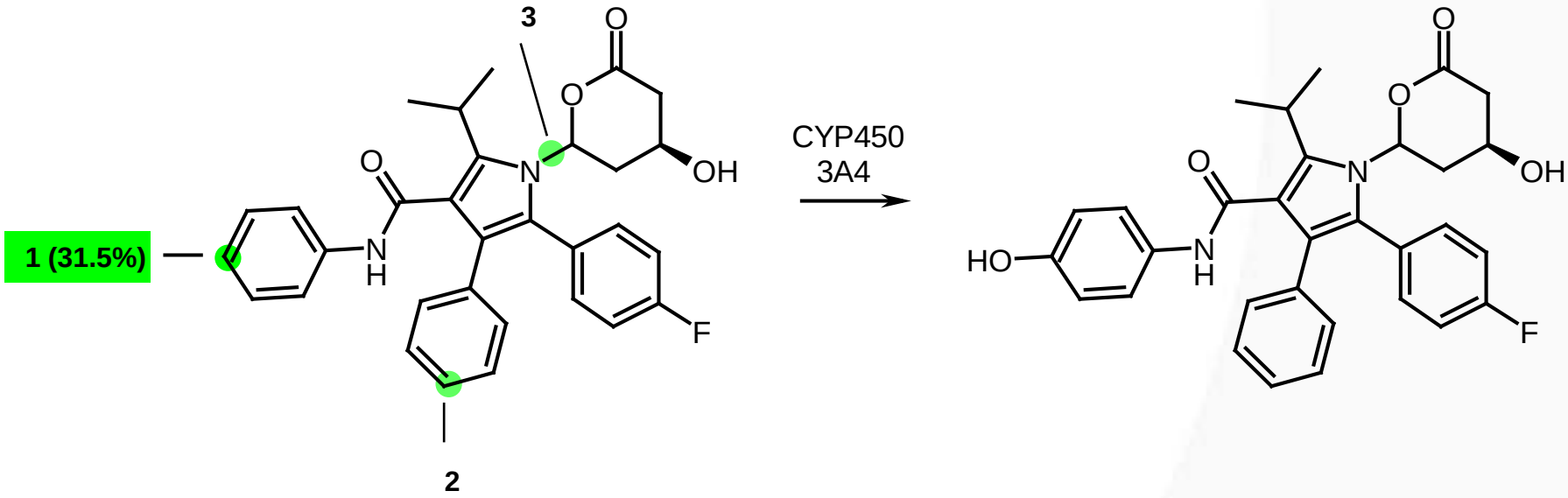
Regioselectivity of aromatic hydroxylation

- **Mono substituted ring**
  - ***Ortho hydroxylation (●)***
  - ***Meta hydroxylation (●)***
  - ***Para hydroxylation (●)***
- **1,4-substituted ring (● , ortho to first and meta to second substituent)**

Predicted Ranks and Probabilities of Atorvastatin Lactone Metabolites



Experimentally observed Metabolite of Atorvastatin Lactone



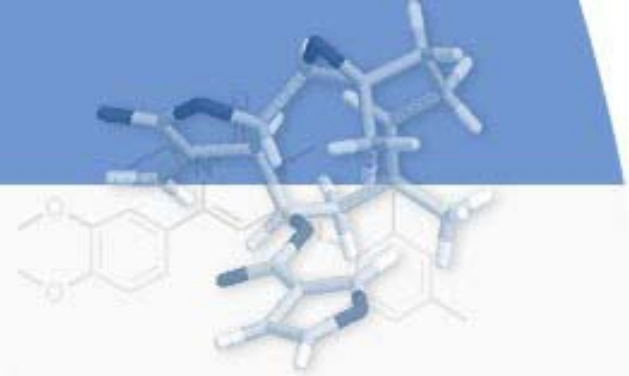
- **Metabolite predicted for atorvastatin with highest rank corresponds to the experimental observations.**

Molecular Networks
Inspiring Chemical Discovery

MOSES.RiskAssessment

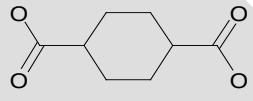
Molecular Networks GmbH
Henkestraße 91
91052 Erlangen, Germany
www.molecular-networks.com

Areas of Applications



- **Hazard and risk assessment of chemicals**
- **Product safety of pharmaceuticals, cosmetics, food ingredients and other chemicals**
- **Computational toxicology**
- **Registration of chemical substances, e.g., REACH initiative**
- **Compound profiling**

Workflow of Risk Assessment



Chemical Speciation → **Collection of Data** → **Categorization Prediction** → **PBT Assessment**

- query
- representation

- reactivity
- degradation
- metabolism

- phys-chem prop
- toxicity
- biological assays

- get data
- read-across
- QSAR prediction

- biodegradation...
- eco-toxicity...
- human health..

Persistence
Bioaccumulation
Toxicity

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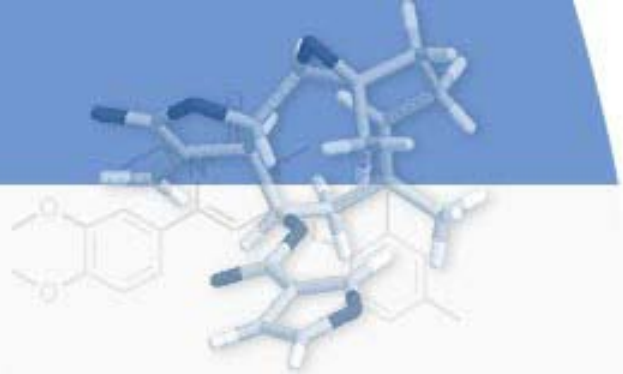
Courtesy of Dr. Chihae Yang.

Application Example



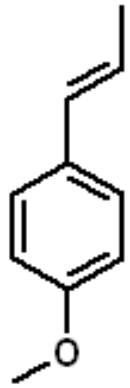
- **Priority-based Assessment of Food Additives (PAFA) by FDA**
- **PAFA contains administrative, chemical and toxicological information on over 2,000 substances directly added to food**
- **Dataset as of July 14, 2010**

Application Example: trans-Anethole

Microsoft Excel - CAS_1-Docnum_1_to_8486-14July2010.xls [Schreibgeschützt]

CAS #1- Docnum 1 to 8486

Doc #	CAS #	Main Term	Doc Type	CFR REG #	ADI	Comments	Cedi	Chemical Functior	Sortterm
0077	004180238	TRANS-ANETHOLE	ASP	182.60				(D) Direct	ANETHOLE
0077	004180238	TRANS-ANETHOLE	ASP	182.60				(F) Flavor	ANETHOLE
0077	004180238	TRANS-ANETHOLE	ASP	182.60				(G) Gras	ANETHOLE



Doc #	Study	Completeness	Effect #1	Source	Lel	Hnel	Unit	Year
77	25	C	GENOTOXIC IN PRESENCE OF EXOGENOUS METABOLIC ACTIVATION	MUTAT RES 101:127-140	,03		mg/plate	1982
77	25.1	C	NO EFFECTS	MUTAT RES 101:127-140		,6	mg/plate	1982
77	25.2	C	GENOTOXIC IN ABSENCE OF EXOGENOUS METABOLIC ACTIVATION	MUTAT RES 101:127-140	10,		mg/plate	1982
77	26	C	NO EFFECTS	BULL ENVIRON CONTAM TOXIC		,05	mg/plate	1982
77	27	C	NO EFFECTS	ENVIRON MUTAGEN 8 (SUPPL 7		,28	mg/plate	1986
77	34	C	CYTOTOXIC (LD50 IS LESS THAN 5 MILLIMOLAR)	FOOD CHEM TOXICOL 30:4	1,	,5	mM	1992
77	40	C	NO EFFECTS	FOOD CHEM TOXICOL 34:337-3		,1	mM	1996
77	40.1	C	NO EFFECTS	FOOD CHEM TOXICOL 34:337-3		500,	mg/kg bw	1996
77	41	C	NO EFFECTS	MUTAT RES 325:129-136		1,	mM	1994
77	42	C	NO EFFECTS	MUTAT RES 326:199-209		,75	mg/plate	1995
77	42.1	C	NO EFFECTS	MUTAT RES 326:199-209		,084	mg/plate	1995
77	42.2	C	NO EFFECTS	MUTAT RES 326:199-209				1995

Molecular Networ
Inspiring Chemical Discovery

MOSES.RiskAssessment | Welcome - Mozilla Firefox

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MOSES.RiskAssessment | We...

MOSES RiskAssessment

New Search | Databases | About

Welcome to MOSES.RiskAssessment

Welcome to the *MOSES.RiskAssessment* Demonstration

- Structure searching
- Data searching
  - Chemical exposure information
  - Toxicity studies information
- Analysis
  - TTC and QSAR analysis
- Toxicity prediction
- Metabolism prediction

An Expert System for Chemical Evaluation and Risk Estimation System

Start the demo.

Please start the demo by entering the Query page.

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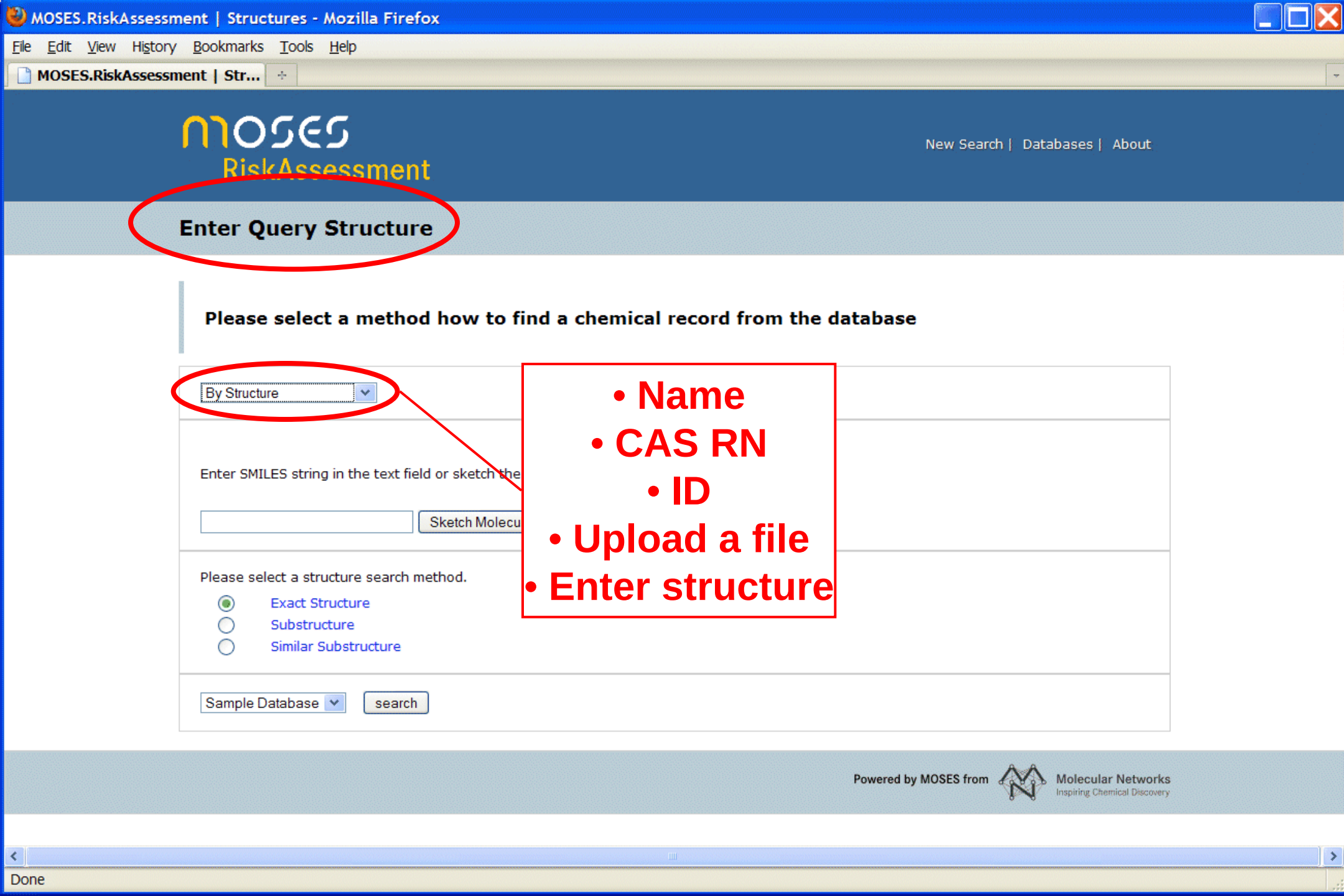
Done


MOSES.RiskAssessment | Structures - Mozilla Firefox
File Edit View History Bookmarks Tools Help
MOSES.RiskAssessment | Str...
MOSES RiskAssessment
New Search | Databases | About
Enter Query Structure
Please select a method how to find a chemical record from the database
By Structure
Enter SMILES string in the text field or sketch the
Sketch Molecu
Please select a structure search method.
Exact Structure
Substructure
Similar Substructure
Sample Database
search
• Name
• CAS RN
• ID
• Upload a file
• Enter structure
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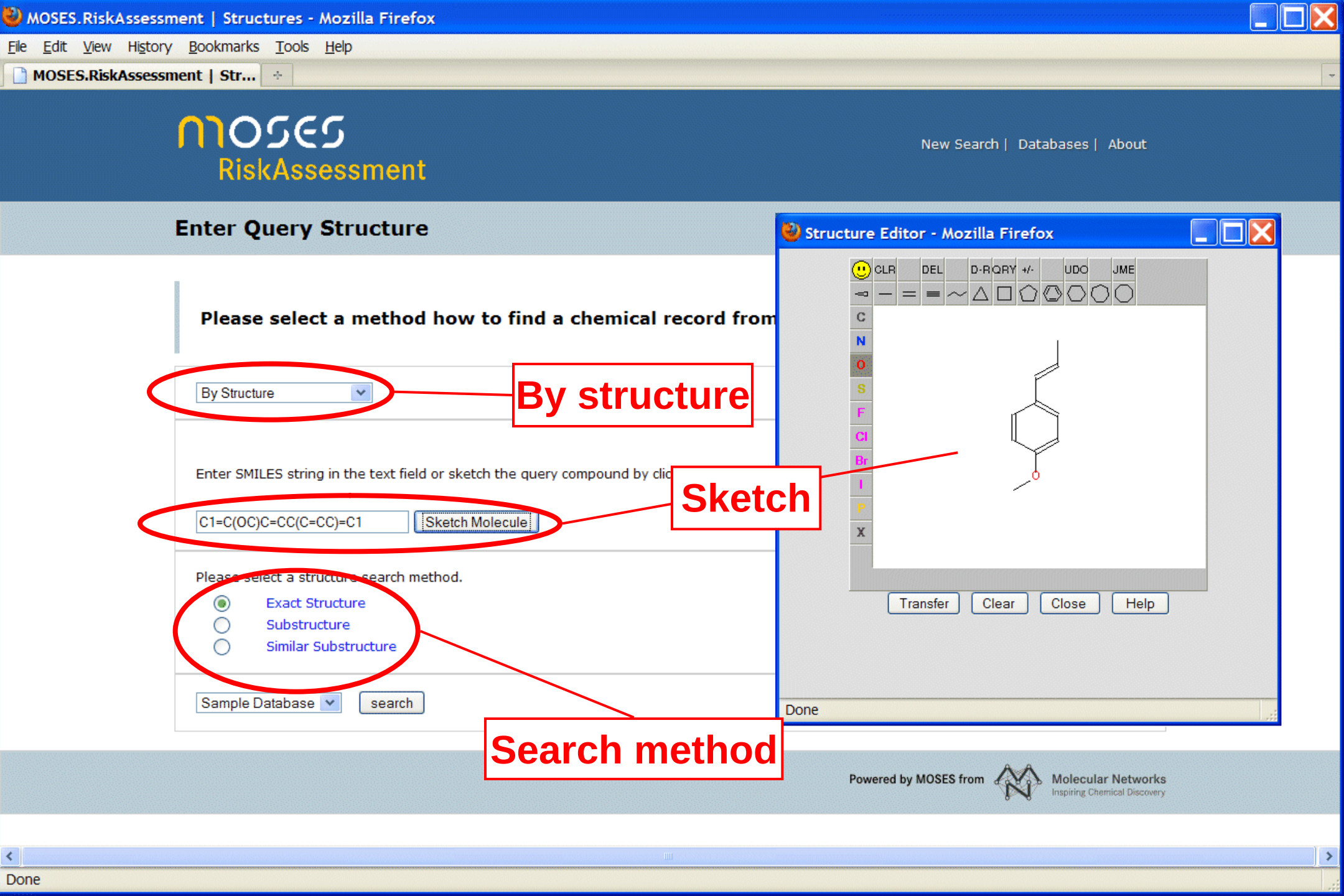
Done


MOSES.RiskAssessment | Structures - Mozilla Firefox
File Edit View History Bookmarks Tools Help
MOSES.RiskAssessment | Str...
MOSES RiskAssessment
New Search | Databases | About
Enter Query Structure
Please select a method how to find a chemical record from
By Structure
By structure
Enter SMILES string in the text field or sketch the query compound by clic
C1=C(OC)C=CC(C=CC)=C1
Sketch Molecule
Sketch
Please select a structure search method.
Exact Structure
Substructure
Similar Substructure
Search method
Sample Database
search
Structure Editor - Mozilla Firefox
CLR DEL D-R QRY +/- UDO JME
C N O S F Cl Br I P X
Transfer Clear Close Help
Done
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Done

MOSES.RiskAssessment | Query Results - Mozilla Firefox

File Edit View History Bookmarks Tools Help

MOSES.RiskAssessment | Qu...

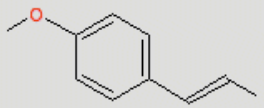
MOSES RiskAssessment

New Search | Databases | About

Query Results

Structure found in the database.

trans-Anethole; Benzene, 1-methoxy-4-(1E)-1-propenyl-; (E)-Anethole; Anisole, p-propenyl-, (E)- (8CI); Anisole, p-propenyl-, trans-; Benzene, 1-methoxy-4-(1-propenyl)-, (E)-



Compound Information

ID	2208
CAS-RN	4180-23-8
Trade Name	
Chemical Name	trans-Anethole
Substance Use Types	Flavoring agent

Show Ames Data

Compound Information

View summarized toxicity data: show/hide

Generate a report for the database record.

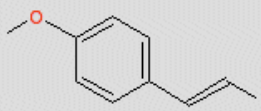
Next steps.

Select the next step to be performed.

Done

Structure found in the database.

trans-Anethole; Benzene, 1-methoxy-4-(1E)-1-propenyl-; (E)-Anethole; Anisole, p-propenyl-, (E)- (8CI); Anisole, p-propenyl-, trans-; Benzene, 1-methoxy-4-(1-propenyl)-, (E)-



Compound Information

ID	2208
CAS-RN	4180-23-8
Trade Name	
Chemical Name	trans-Anethole
Substance Use Types	Flavoring agent

Hide Details

Study Information 1, Source: cfsan-pafa

Study Information

FARM Status:	Document Type:	Document Number:	Document Status:	Review Date:	Results found:
			Does not meet at least core standards		8

#	Study Type	Species	Strain	Metabolic Activation	All Doses	Dose Unit	Test Cytotoxicity	Test Precipitation	Test Call	Study Call
1	Bacterial mutagenesis	Salmonella typhimurium	TA98	Absent	280.0 micro-g/plate	micro-g/plate			Negative	Negative
2	Bacterial mutagenesis	Salmonella typhimurium	TA100	Absent	280.0 micro-g/plate	micro-g/plate			Negative	Negative
3	Bacterial mutagenesis	Salmonella typhimurium							Negative	Negative
4	Bacterial mutagenesis	Salmonella typhimurium	TA1537	Absent	280.0 micro-	micro-g/plate			Negative	Negative

Test data – strain level

MOSES.RiskAssessment | Query Results - Mozilla Firefox

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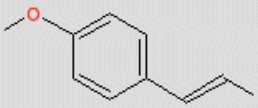
MOSES.RiskAssessment | Qu...

Structure found in the database.

trans-Anethole; Benzene, 1-methoxy-4-(1E)-1-propenyl-; (E)-Anethole; Anisole, p-propenyl-, (E)- (8CI); Anisole, p-propenyl-, trans-; Benzene, 1-methoxy-4-(1-propenyl)-, (E)-



Compound Information

ID	2208
CAS-RN	4180-23-8
Trade Name	
Chemical Name	trans-Anethole
Substance Use Types	Flavoring agent

Show Ames Data

Generate a report for the database record.

Report generation

Next steps.

Select the next step to be performed.

- Run analog search
- Run TTC analysis
- Run toxicity prediction
- Run metabolism prediction

- Analog search
- TTC analysis
- Toxicity prediction
- Metabolism prediction

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Done

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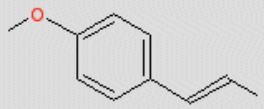

Compound Information

ID	2208
CAS-RN	4180-23-8
Trade Name	
Chemical Name	trans-Anethole
Substance Use Types	Flavoring agent

Show Ames Data

Generate a report for the database record.

Next steps.

Select the next step to be performed.

- Run analog search
- Run TTC analysis
- Run toxicity prediction
- Run metabolism prediction

Similarity criteria: MDL/Symyx MACCS keys

Cut off: 70

Run

Analog searching

Similarity criteria – MDL fingerprints

Specify cut off

Run search

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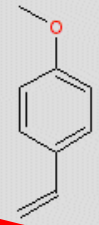
Done

Analogs found in the database.

60 analogs found in the database. (The first 10 most similar analogs are shown below).

Include this compound into TTC analysis.

Similarity score: **92 %**



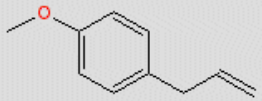
Compound Information

ID	6532
CAS-RN	637-69-4
Trade Name	
Chemical Name	4-Methoxystyrene
Substance Use Types	

Show Ames Data

Include this compound into TTC analysis.

Similarity score: **92 %**



Compound Information

ID	776
CAS-RN	140-67-0
Trade Name	
Chemical Name	Estragole
Substance Use Types	Flavoring agent

Show Ames Data

Include this compound into TTC analysis.

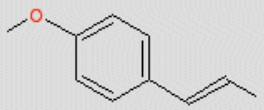
List with analogs

Analogs with data

MOSES.RiskAssessment | Query Results - Mozilla Firefox

File Edit View History Bookmarks Tools Help

MOSES.RiskAssessment | Qu...



Compound Information

ID	2208
CAS-RN	4180-23-8
Trade Name	
Chemical Name	trans-Anethole
Substance Use Types	Flavoring agent

Show Ames Data

Generate a report for the database record.

Next steps.

TTC analysis

Select the next step to be performed.

- Run analog search
- Run TTC analysis
- Run toxicity prediction
- Run metabolism prediction

TTC categories

Select the phenotypic endpoint of your interest: Genetic toxicity - bacterial mutagenesis

Select analysis parameters for your own analysis: TTC category

Run

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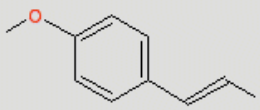
Done

MOSES RiskAssessment

Results of TTC Analysis

TTC analysis for the query compound.

trans-Anethole; Benzene, 1-methoxy-4-(1E)-1-propenyl-; (E)-Anethole; Anisole, p-propenyl-, (E)- (8CI); Anisole, p-propenyl-, trans-; Benzene, 1-methoxy-4-(1-propenyl)-, (E)-



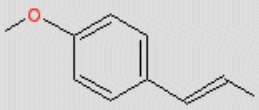
No TTC alerts for that compound.

Run Models for a toxicity prediction

Important note: the prediction may take some time. Please wait until the results are presented ...

Run Models

trans-Anethole; Benzene, 1-methoxy-4-(1E)-1-propenyl-; (E)-Anethole; Anisole, p-propenyl-, (E)- (8CI); Anisole, p-propenyl-, trans-; Benzene, 1-methoxy-4-(1-propenyl)-, (E)-



Compound Information

ID	2208
CAS-RN	4180-23-8
Trade Name	
Chemical Name	trans-Anethole
Substance Use Types	Flavoring agent

Show Ames Data

Generate a report for the database record.

Toxicity prediction

Next steps.

Select the next step to be performed.

- ○ Run analog search
- ○ Run TTC analysis
- ◉ Run toxicity prediction
- ○ Run metabolism prediction

Run

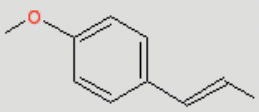
MOSES RiskAssessment

Results for the toxicity prediction

Toxicity prediction for the query compound.

Endpoint: **Genetic toxicity - bacterial mutagenesis**

trans-Anethole; Benzene, 1-methoxy-4-(1E)-1-propenyl-; (E)-Anethole; Anisole, p-propenyl-, (E)- (8CI); Anisole, p-propenyl-, trans-; Benzene, 1-methoxy-4-(1-propenyl)-, (E)



Probability of being positive	Prediction
0.222	negative

Show Model Details

Further steps.

MOSES.RiskAssessment | Query Results - Mozilla Firefox

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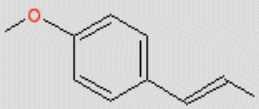
MOSES.RiskAssessment | Qu...

trans-Anethole; Benzene, 1-methoxy-4-(1E)-1-propenyl-; (E)-Anethole; Anisole, p-propenyl-, (E)- (8CI); Anisole, p-propenyl-, trans-; Benzene, 1-methoxy-4-(1-propenyl)-, (E)-



Compound Information

ID	2208
CAS-RN	4180-23-8
Trade Name	
Chemical Name	trans-Anethole
Substance Use Types	Flavoring agent

Show Ames Data

Generate a report for the database record.

Metabolism prediction

Next steps.

Select the next step to be performed.

- ○ Run analog search
- ○ Run TTC analysis
- ○ Run toxicity prediction
- ◉ Run metabolism prediction

Run

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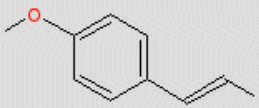
Done

Metabolite Prediction

Parent compound.



Compound Information

Name trans-Anethole; Benzene, 1-methoxy-4-(1E)-1-propenyl-; (E)-Anethole; Anisole, p-propenyl-, (E)- (8CI); Anisole, p-propenyl-, trans-; Benzene, 1-methoxy-4-(1-propenyl)-, (E)-

Isoform CYP3A4

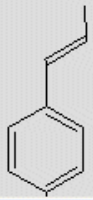
Metabolites.

Generated 4 metabolites.

List with metabolites

Include this compound into toxicity prediction.

Metabolite no. 1



Compound Information

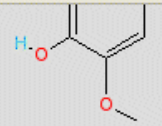
Rule O_Demethylation_ArOMe_short

Probability 0.27

MOSES.Metabolism | Metabolite Prediction - Mozilla Firefox

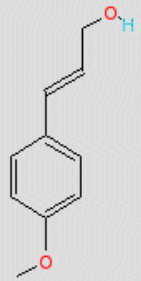
File Edit View History Bookmarks Tools Help

MOSES.Metabolism | Metabol...



Include this compound into toxicity prediction.

Metabolite no. 4



Compound Information

Rule AliphaticHydroxylation_primCnextsp2C_short

Probability 0.04

Run toxicity prediction

Run toxicity prediction with selected compounds.
The query compound is always included in the prediction.

Select all metabolites for toxicity prediction.

Analyze

Toxicity prediction for query compound and all metabolites

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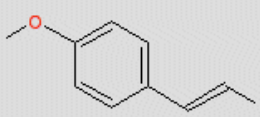
Done

Toxicity prediction for the query compound.

Endpoint: **Genetic toxicity - bacterial mutagenesis**

trans-Anethole; Benzene, 1-methoxy-4-(1E)-1-propenyl-; (E)-Anethole; Anisole, p-propenyl-, (E)- (8CI); Anisole, p-propenyl-, trans-; Benzene, 1-methoxy-4-(1-propenyl)-, (E)-

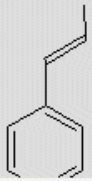


Probability of being positive	Prediction
0.222	negative

Show Model Details

Toxicity prediction for the set of 4 metabolites

C9H10O

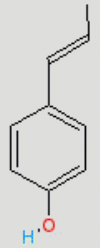


Probability of being positive	Prediction
0.165	negative

Show Model Details

Toxicity prediction for the set of 4 metabolites

C9H10O

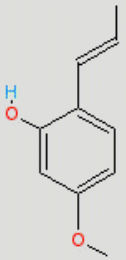


Probability of being positive	Prediction
0.165	negative

Show Model Details

no. 1

C10H12O2



Probability of being positive	Prediction
0.204	negative

Show Model Details

no. 2

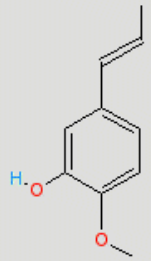
C10H12O2

MOSES.RiskAssessment | Toxicity Prediction Results - Mozilla Firefox

File Edit View History Bookmarks Tools Help

MOSES.RiskAssessment | To...

C10H12O2

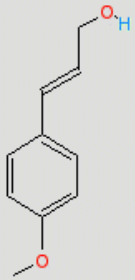


Probability of being positive	Prediction
0.162	negative

Show Model Details

no. 3

C10H12O2



Probability of being positive	Prediction
0.316	intermediate

Show Model Details

no. 4

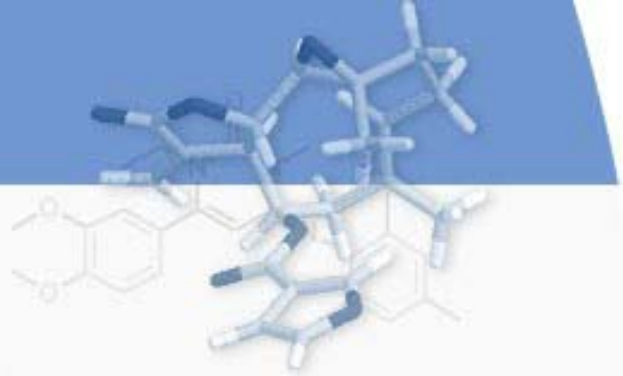
Toxic after metabolic activation?

Further steps.

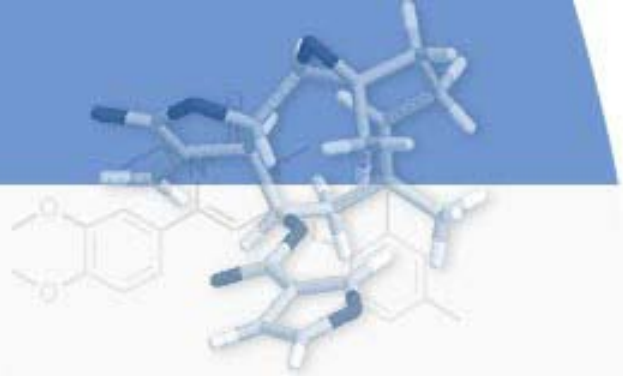
- **Generate a report** for the session.
- Run a new search.

Done

Features & Functionality

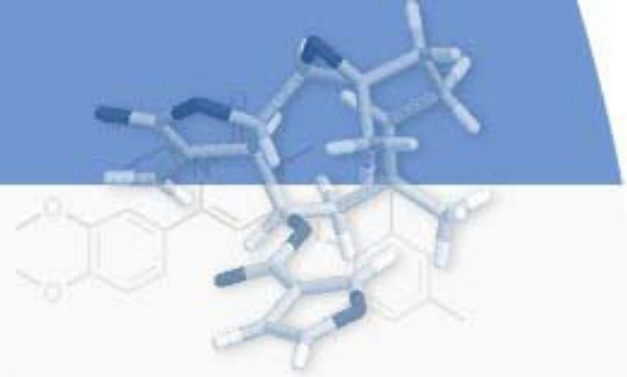


- Knowledge base for hazard and risk assessment of chemicals
- Database lookup by text-based, analog and similarity searches
- Retrieval of available study information for query compound and analogs
- Generation and evaluation of metabolites of query and analogs (including CYP isoform specificity)
- Analysis tools for query, analogs and their metabolites
- TTC analysis
- QSAR predictions of toxicity endpoints (e.g., Ames mutagenicity)
- Report generation
- Fully web-based, easy-to-use user interface



Metabolism in the ToxCast Dataset

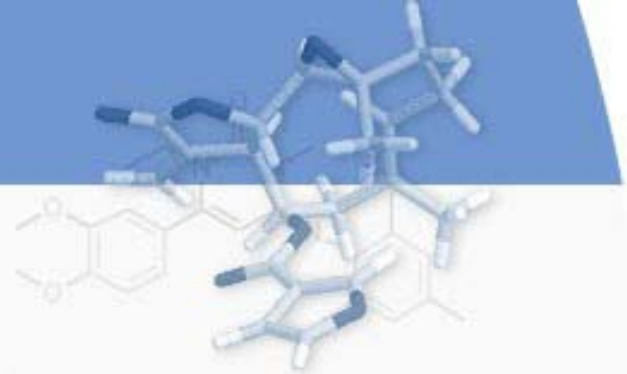
Identification of Parent/Metabolite Pairs in the ToxCast Dataset



- **Approach**
  - ***Generate all conceivable metabolites for the compounds in the ToxCast dataset with MOSES.Metabolism***
  - ***Determine the intersection of the set of all generated metabolites with the set of compounds in the ToxCast dataset***

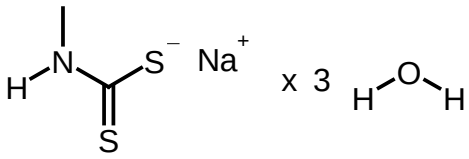
- **Results**
  - ***MOSES.Metabolism generated 1826 metabolites for the 309 unique compounds from the ToxCast dataset (approx. six metabolites per parent compound on average)***
  - ***Fourteen parent/metabolite pairs could be identified***

Most Frequently Observed Reaction Types in ToxCast

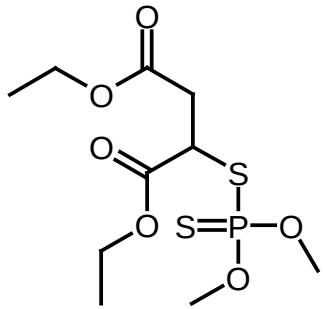


Aromatic hydroxylation of a phenyl ring:	543
O-Dealkylation:	99
Ester hydrolysis:	77
N-Dealkylation:	71
Aromatic amine oxidation:	64
Amide hydrolysis:	63
Aliphatic hydroxylation of a primary carbon atom next to a secondary carbon atom:	59
Aromatic hydroxylation of 1,2-substituted aromatic ring in 4 position:	52
O-Sulphation:	52

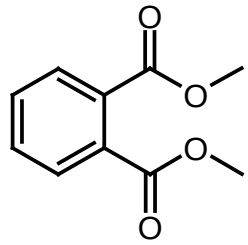
Parent Compounds



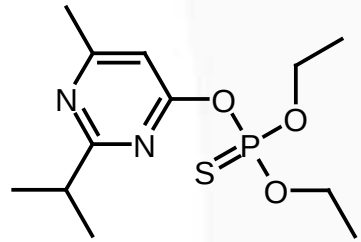
Metam-sodium hydrate



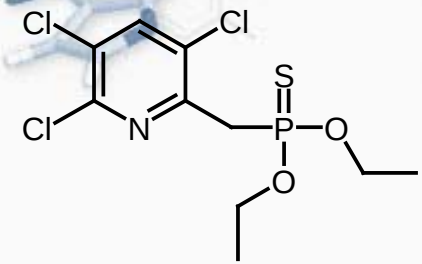
Malathion



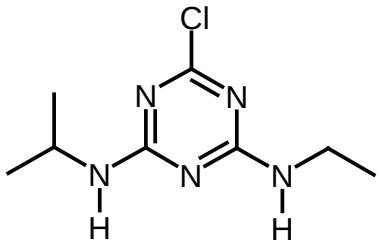
Dimethylphthalate



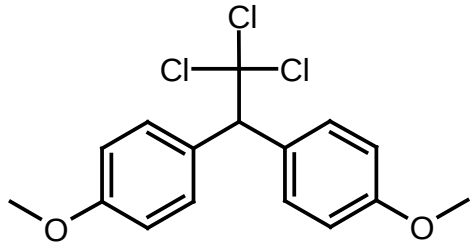
Diazinon



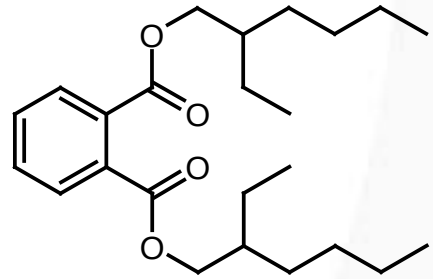
Chlorpyrifos



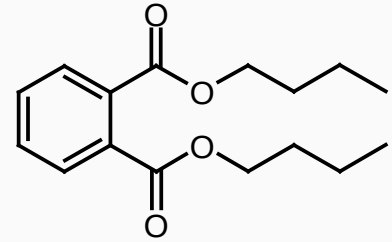
Atrazine



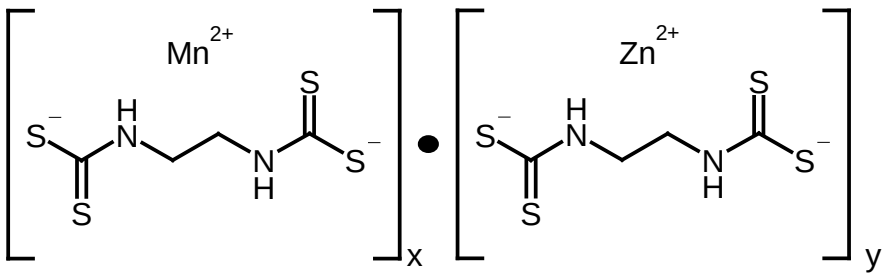
Methoxychlor



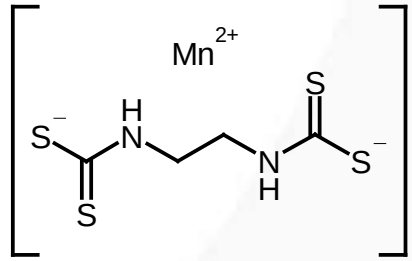
Diethylhexylphthalate



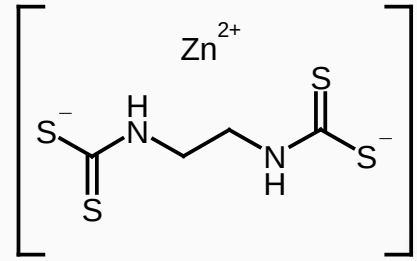
Dibutylphthalate



Mancozeb

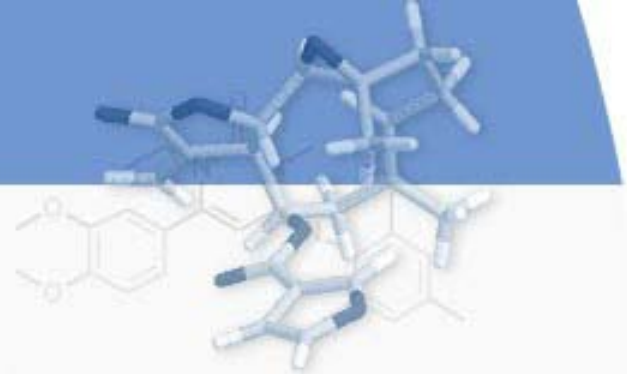


Maneb



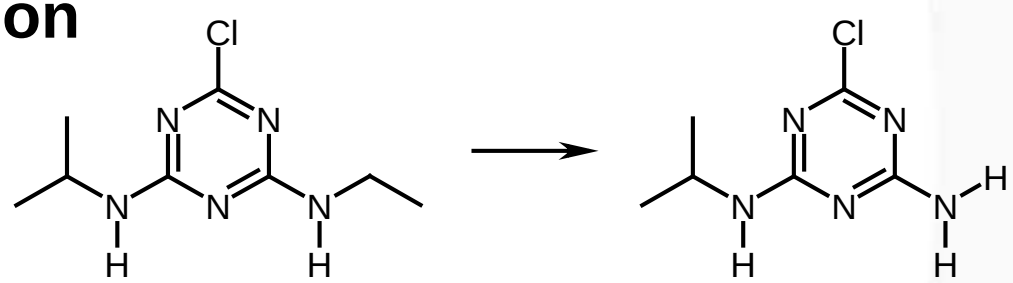
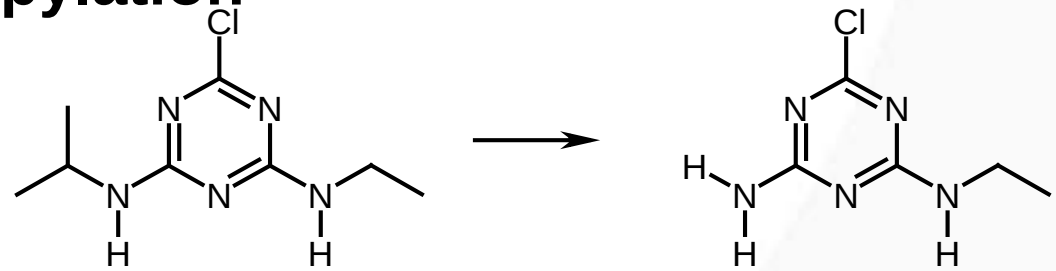
Metiram-zinc

Extension of Reaction Rules

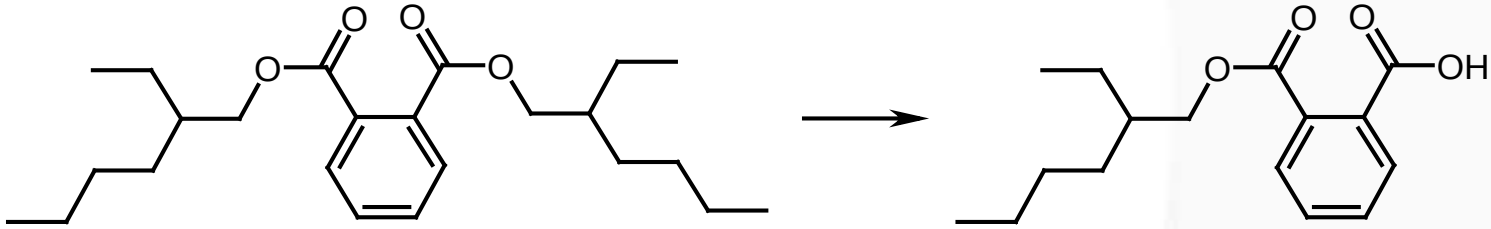
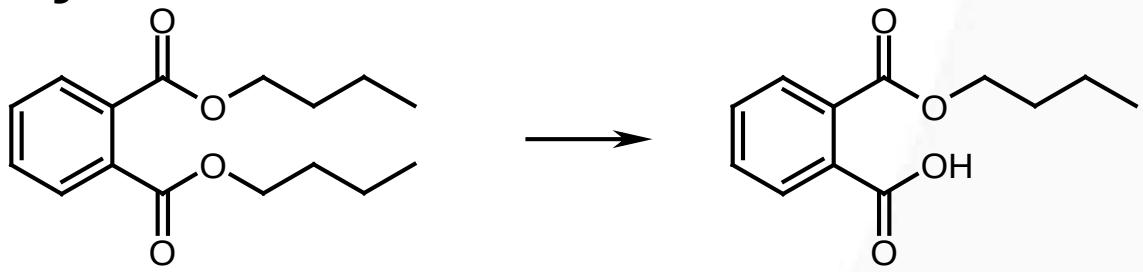


- **Reaction rules for oxidative desulfuration were added to MOSES.Metabolism in order to identify the following parent compound metabolite pairs in the ToxCast data set:**
  - ***Malathion – Malaoxon***
  - ***Diazinon – Diazoxon***
  - ***Chlorpyrifos – Chlorpyrifos oxon***
  - ***Metam-sodium hydrate – Methylisothiocyanate***

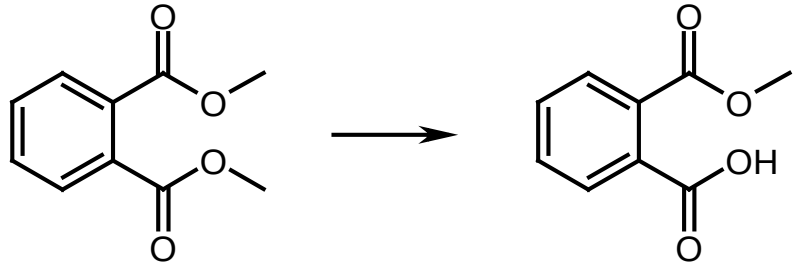
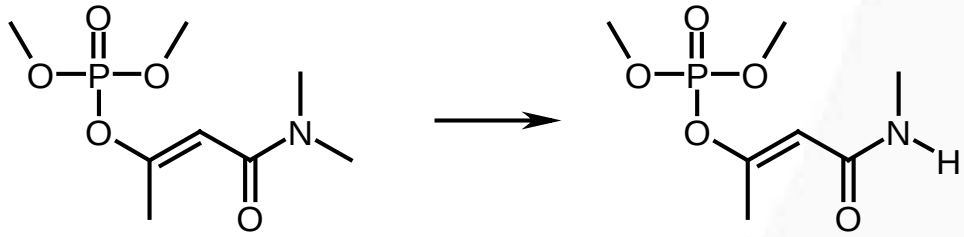
Parent/Metabolite Pairs 1 & 2

- **N-Deethylation**
  - 
  - ***Probability: 0.59*** ***Rank: 1***
- **N-Deisopropylation**
  - 
  - ***Probability: 0.31*** ***Rank: 2***

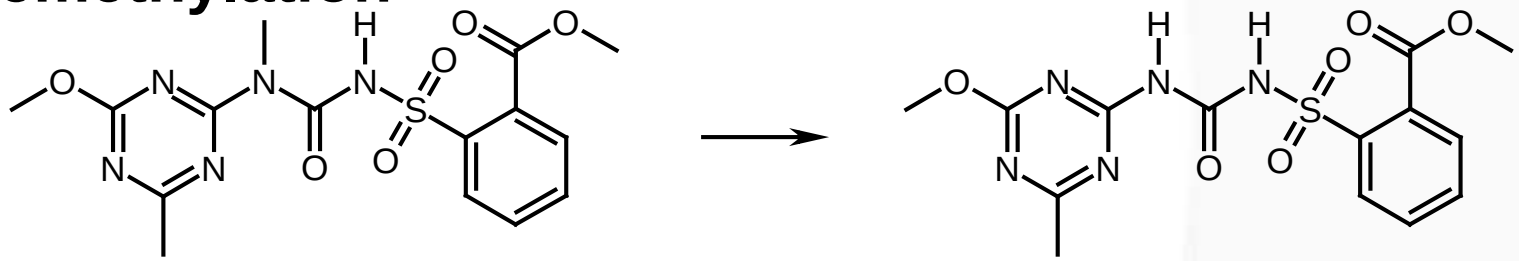
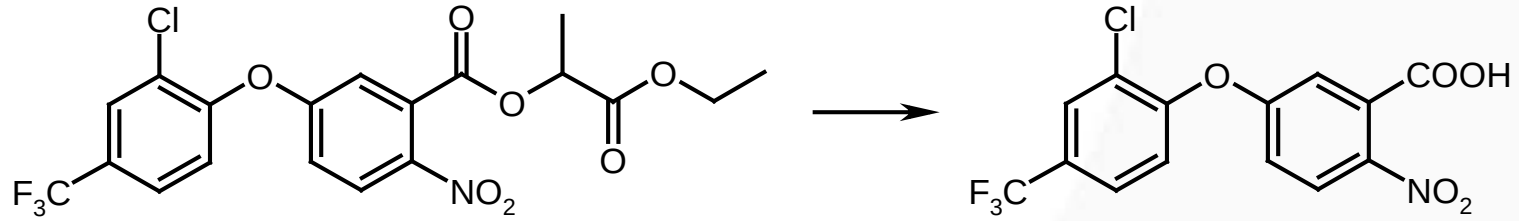
Parent/Metabolite Pairs 3 & 4

- **Esterhydrolysis**
  - 
  - ***Probability: 0.67*** ***Rank: 1***
- **Esterhydrolysis**
  - 
  - ***Probability: 0.67*** ***Rank: 1***

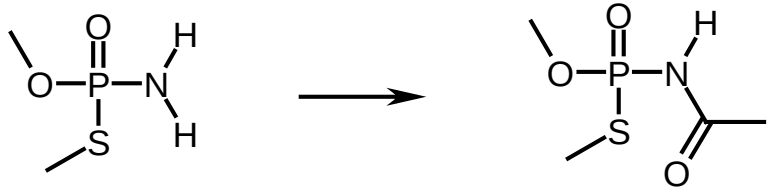
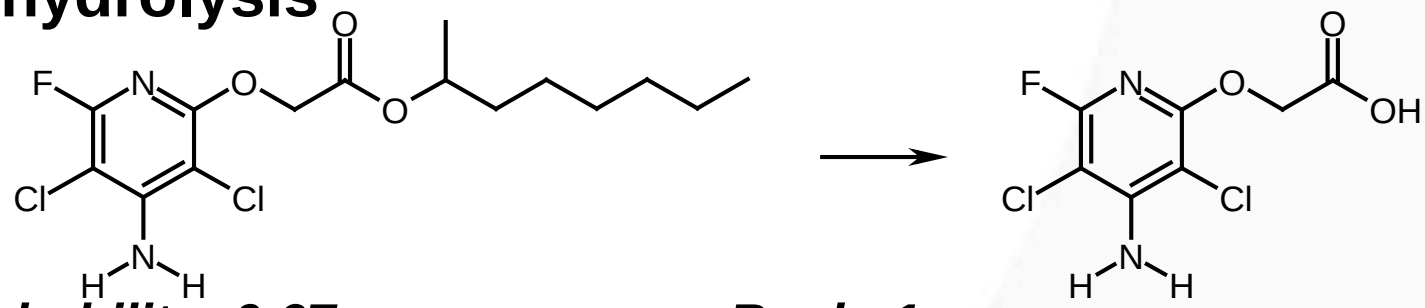
Parent/Metabolite Pairs 5 & 6

- **Esterhydrolysis**
  - 
  - ***Probability: 0.67*** ***Rank: 1***
- **N-Demethylation of $RNMe_2$**
  - 
  - ***Probability: 0.41*** ***Rank: 1***

Parent/Metabolite Pairs 7 & 8

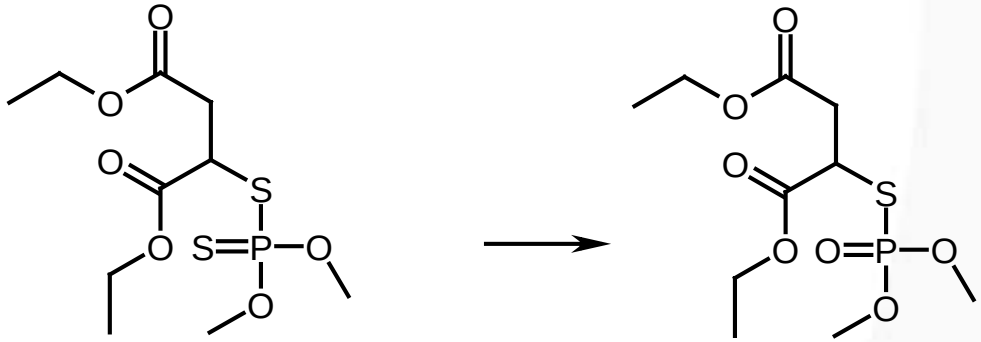
- **N-Demethylation**
  - 
  - ***Probability: 0.17*** ***Rank: 3***
- **Esterhydrolysis**
  - 
  - ***Probability: 0.67*** ***Rank: 1***

Parent/Metabolite Pairs 9 & 10

- **N-Acetylation of heterobonded NH_2**
  - 
  - ***Probability: 0.08*** ***Rank: 1***
- **Esterhydrolysis**
  - 
  - ***Probability: 0.67*** ***Rank: 1***

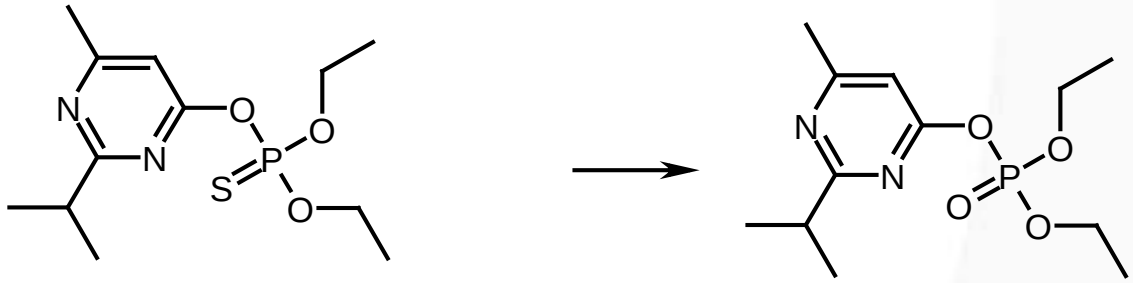
Parent/Metabolite 11

- **Oxidative desulfuration**
  - ***Malathion – Malaoxon***



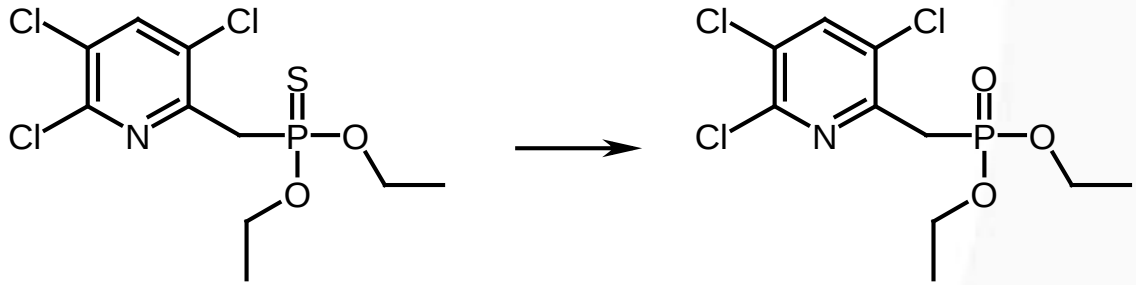
Parent/Metabolite 12

- **Oxidative desulfuration**
  - ***Diazinon – Diazoxon***



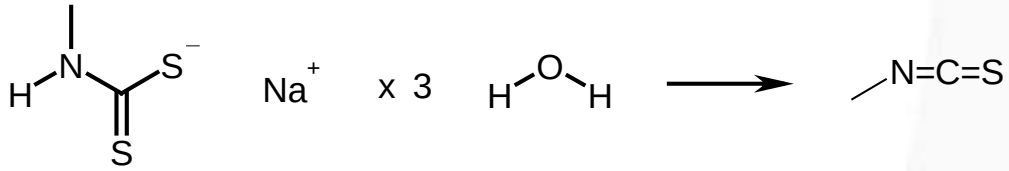
Parent/Metabolite 13

- **Oxidative desulfuration**
  - ***Chlorpyrifos – Chlorpyrifos oxon***

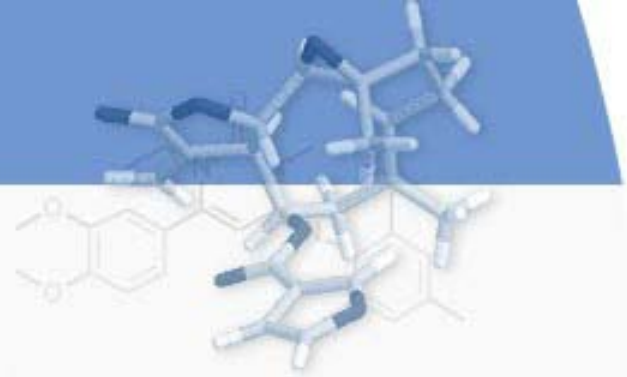


Parent/Metabolite 14

- **Oxidative desulfuration**
  - ***Metam-sodium hydrate – Methylisothiocyanate***



Missing Pairs



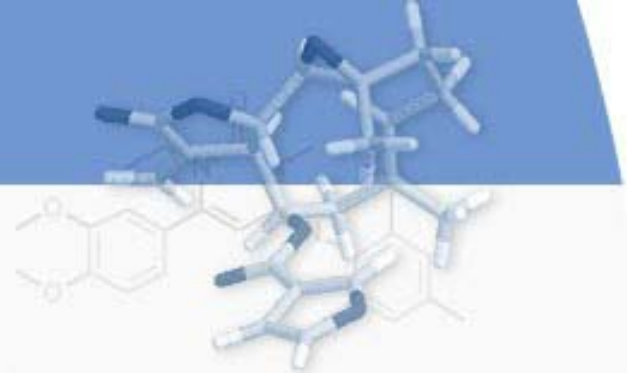
Parent – Metabolite Pairs

- **Mancozeb/Maneb/Metiram – Ethylenethiourea**
- **Methoxychlor – HPTE**

Reason

- **Missing rule; metal complex**
- **O-Demethylation in two positions; rules were only applied ones**

New Descriptors for Metabolic Reactivity

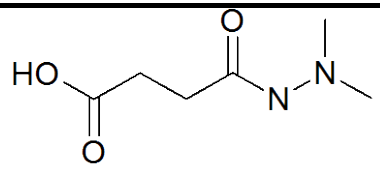
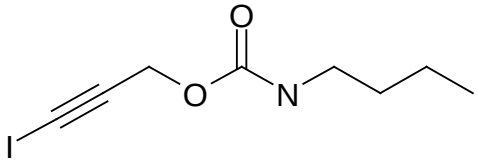


- **Describing chemical structures with *a priori* chemical knowledge on reaction centers and metabolic reactivity**

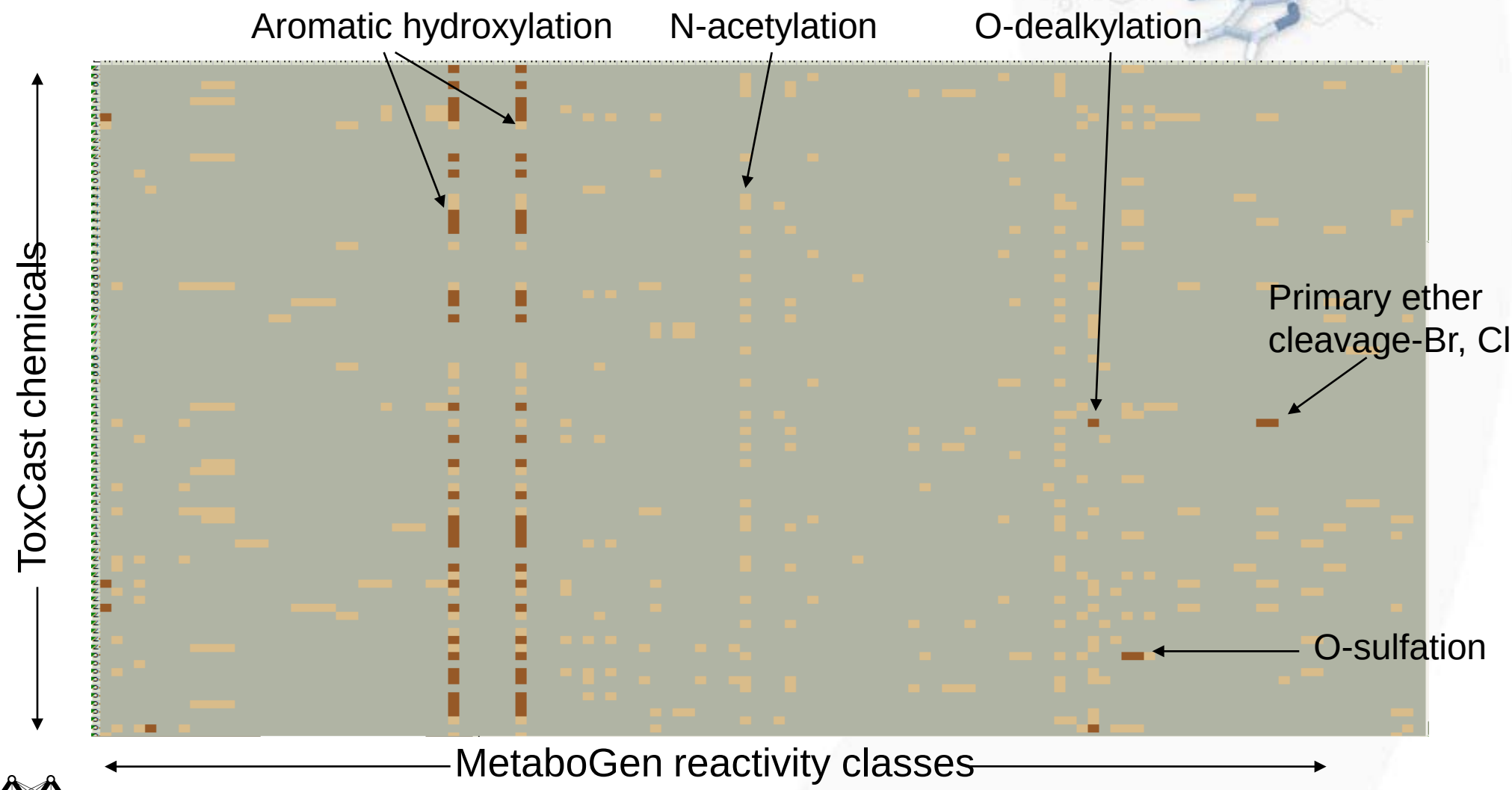
- **Metabolic reactivity classes**
  - ***To describe metabolic fate of chemicals***
  - ***Reaction types***
    - **aromatic hydroxylation, aliphatic hydroxylation, N- and O-dealkylation, hydrolysis (ester, amide), and conjugation reactions (acetylation, sulfation, etc.)**

- **Use of the MOSES.Metabolism rule base for metabolic screening (metabolic profile; metabolic fingerprints)**

Extract of the Metabolic Reactivity Matrix of the ToxCAST Data Set

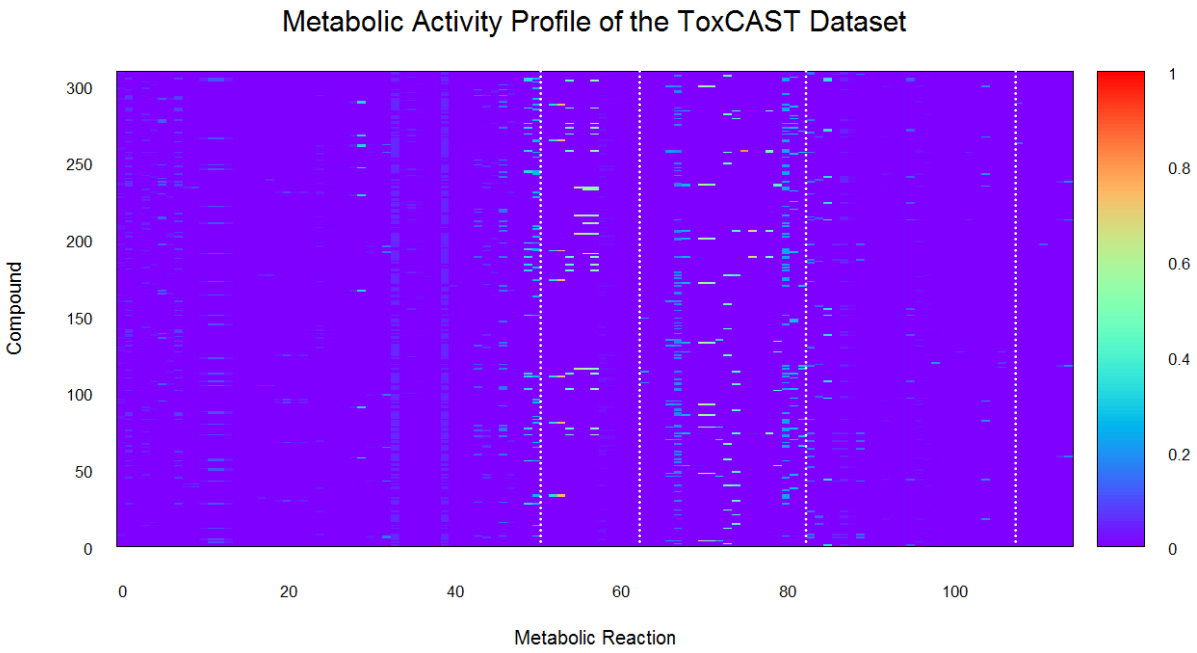
DSSTox_CID	Structure	MetaboGen total counts	Aromatic hydroxylation	Aliphatic hydroxylation (prim. C next sec. C)	Aliphatic hydroxylation (sec. C next to CH3)	N-Demethylation R-NMe2	O-Sulphation	N-Acetylation R-NH2	…
370		2	0	0	0	1	1	0	…
8038		6	0	1	1	0	0	0	…

Fingerprint View of Metabolic Reactivity Classes



Metabolic Reactivity Profile of the ToxCast Dataset

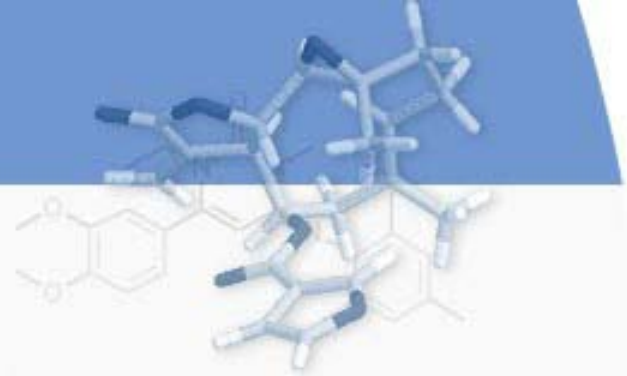
Probability of conceivable metabolic reactions



Reactions	Type
1-48	Hydroxylation
49-62	Hydrolysis
63-83	N-,O-Dealkylation
84-109	Conjugation
110-115	others

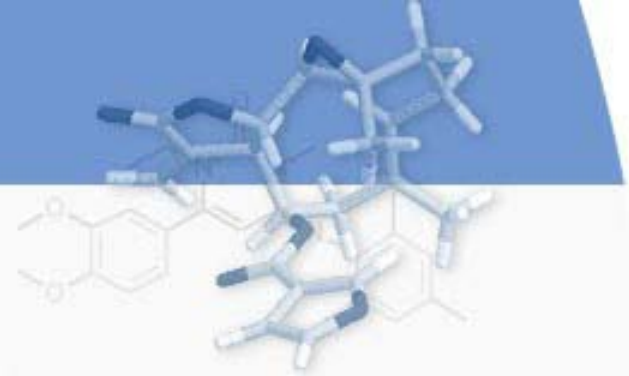
309 compounds; 115 reaction rules from MOSES.Metabolism (2009-06-11)

Metabolic Reactivity Profile



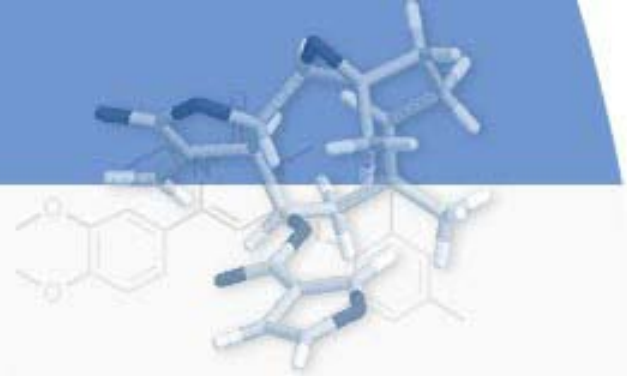
- **The Metabolic Reactivity Profiles provide an easy method for rapidly screening for potential metabolites in large datasets of compounds**

Molecular Networks



- **Innovation company for Chemoinformatics**
  - ***"Chemoinformatics: the processing of chemical information by informatics tools"***
- **Mission statement**
  - ***Increasing the quality and productivity of discoveries in chemical, pharmaceutical and biotechnology R&D***
- **Products and services**
  - ***Broad range of scientific software products***
  - ***Consulting and research services***
  - ***Contract development***

Molecular Networks Provides Applications for ...



- **Drug design and property prediction**
- **Synthesis design and reaction prediction**
- **Risk Assessment of Chemicals**
- **Prediction of metabolism**
  - ***Endogenous metabolism***
  - ***Metabolism of xenobiotics (drugs, agrochemicals, ...)***
- **Design of biotechnological processes**
- **Data warehousing & mining**
- **Handling, processing and manipulation of chemical structure, reaction and related information**

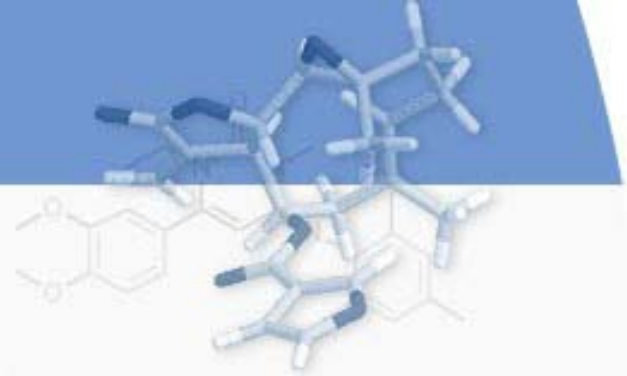
Acknowledgements

- Dr. Aleksey Tarkhov
- Dr. Bruno Bienfait
- Dr. Christof Schwab
- Dr. Jörg Marusczyk
- Dr. Lothar Terfloth
- Dr. Oliver Sacher
- Dr. Thomas Kleinöder

and my former coworkers
at Computer-Chemie-Centrum
University of Erlangen

Collaboration

- Dr. Chihae Yang



Molecular Networks GmbH

www.molecular-networks.com