

Predict Metabolites of Compounds

Software/web servers to use:

SMARTCyp web server (predicts site of metabolism): www.farma.ku.dk/smartcyp

ToxTree 2.5 with SMARTCyp module and metabolite prediction

Optional:

Bioclipse with installed MetaPrint2D module. (Can be found in *Help : Software Updates...* in Bioclipse)

PubChem (for locating smiles and structures for other compounds): <http://pubchem.ncbi.nlm.nih.gov/>

SMARTCyp basics:

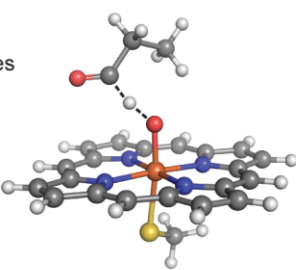
Prediction of Cytochrome P450 mediated metabolism. (ca. 90% of Phase I metabolism)

Based on purely computational data, no experimental data used to create the model.

Model Building

Atom Reactivity Library

A. Calculate Quantum Chemical Reference Energies
Calculate transition state energies using density functional theory



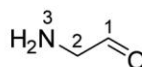
B. Define SMARTS Rules
Group calculations by fragments and calculate average energies

CC=O C1=CC=C(C=C1)C=O \Rightarrow [CX3H1](=O)[#6]
40.2 kJ/mol

Software execution

SMARTCyp

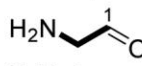
1. Assign Energies By SMARTS matching



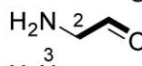
Atom	SMARTS	Energy
1	<chem>[CX3H1](=O)[#6]</chem>	40.2
2	<chem>[CX4][N]</chem>	39.8
3	<chem>[N^3][H1,H2]</chem>	54.1

2. Compute Accessibility Descriptor

$$A_i = \text{Maxbonds}_i / \text{Maxbonds}_{\text{all}}$$



$$A_1 = 2 / 3 = 0.67$$



$$A_2 = 2 / 3 = 0.67$$



$$A_3 = 3 / 3 = 1.00$$

3. Compute Score and Rank Atoms

$$\text{Score, } S = E - 8A$$

Lowest score gets rank 1

$$S_1 = 40.2 - 8 \cdot 0.67 = 34.84$$

Atom 1 - Rank 2

$$S_2 = 39.8 - 8 \cdot 0.67 = 34.44$$

Atom 2 - Rank 1

$$S_3 = 54.1 - 8 \cdot 1.00 = 46.10$$

Atom 3 - Rank 3

MetaPrint2D basics:

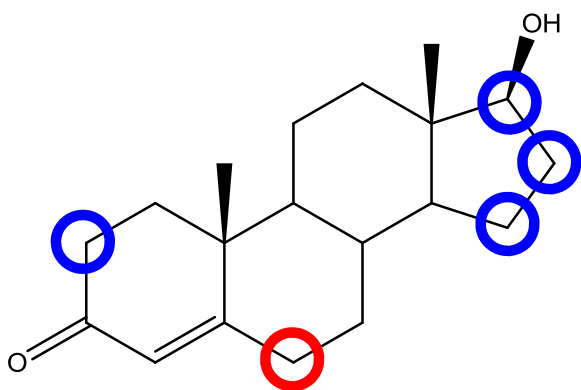
Predictions based upon similarity to compounds/fragments that undergo phase I metabolism according to the Symyx metabolite database. Ask Ola Spjuth about the details.

Examples with excellent SMARTCyp predictions

Major metabolites in red, and minor in blue.

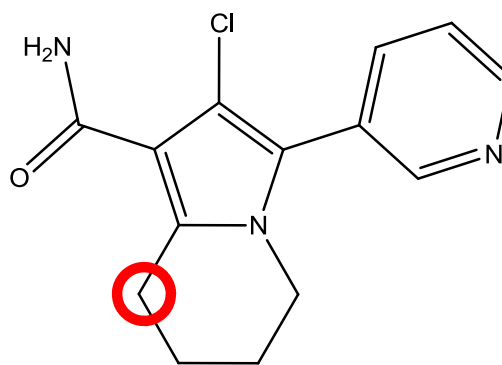
Testosterone

CC12CCC3C(C1CCC2O)CCC4=CC(=O)CCC34C



CMV342

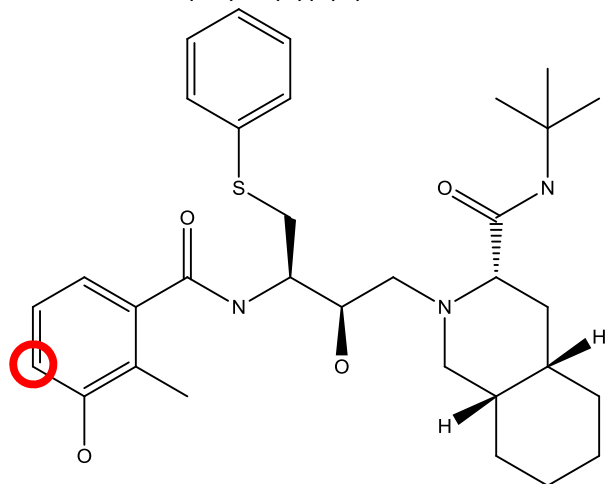
C1CCN2C(=C(C(=C2C3=CN=CC=3)Cl)C(=O)N)C1



Examples with bad SMARTCyp predictions

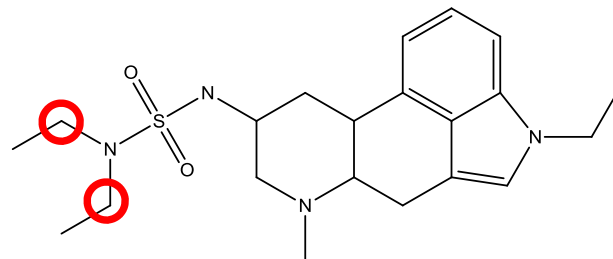
Nelfinavir

CC1=C(C=CC=C1O)C(=O)NC(CSC2=CC=CC=C2)C(CN3C4CCCCC4CC3C(=O)NC(C)(C)C)O



CQA 206-291

CCN1C=C2CC3C(CC(CN3C)NS(=O)(=O)N(CC)CC)C4=C2C1=CC=C4



Limitations of SMARTCyp

Only cytochrome P450 mediated metabolism. (ca. 90% of phase I metabolites)

Highly reactive sites preferred before highly accessible sites.

Ring-openings and dealkylations of tertiary amines are not separated.

Amine nitrogen oxidations predicted too often.

Limitations of the metabolite prediction in ToxTree

Ring-openings suggested too often (because of SMARTCyp rankings).

Very new implementation, not tested against all possible chemical fragments and metabolites.

Examples of toxic compounds activated by P450s

6-aminochrysene: C1=CC=C2C(=C1)C=CC3=C2C=C(C4=CC=CC=C34)N

2-aminoanthracene: C1=CC=C2C=C3C=C(C=CC3=CC2=C1)N

2-aminofluorene: Nc1ccc3c(c1)Cc2ccccc23

MeIQ: CC1=CC2=C(C=CC=N2)C3=C1N(C(=N3)N)C

IQ: n2cccc3c1nc(n(c1ccc23)C)N

Trp-P-1: n3c(c2c1c(cccc1)nc2c(c3N)C)C

3-methoxy-4-aminoazobenzene: COC1=C(C=CC(=C1)N=NC2=CC=CC=C2)N

Aflatoxin B₁: COC1=C2C3=C(C(=O)CC3)C(=O)OC2=C4C5C=COC5OC4=C1

Sterigmatocystin: COC1=C2C(=C3[C@@H]4C=CO[C@@H]4OC3=C1)OC5=C(C2=O)C(=CC=C5)O

And lots of polyaromatic hydrocarbons form epoxide diols through sequential oxidations by P450s, and then react with DNA, for example:

benzopyrene: c1ccc2c(c1)cc3ccc4cccc5c4c3c2cc5

benzo[a]anthracene: c34cc2ccc1cccc1c2cc3cccc4