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)

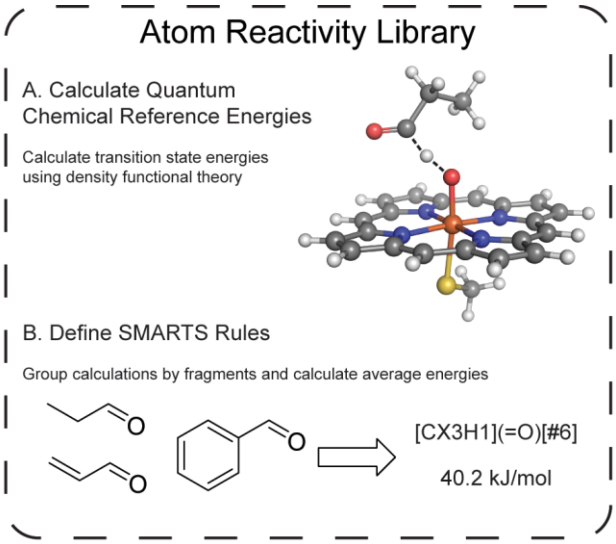
PubChem (for locating smiles and structures for other compounds): http://pubchem.ncbi.nlm.nih.gov/

SMARTCyp basics:

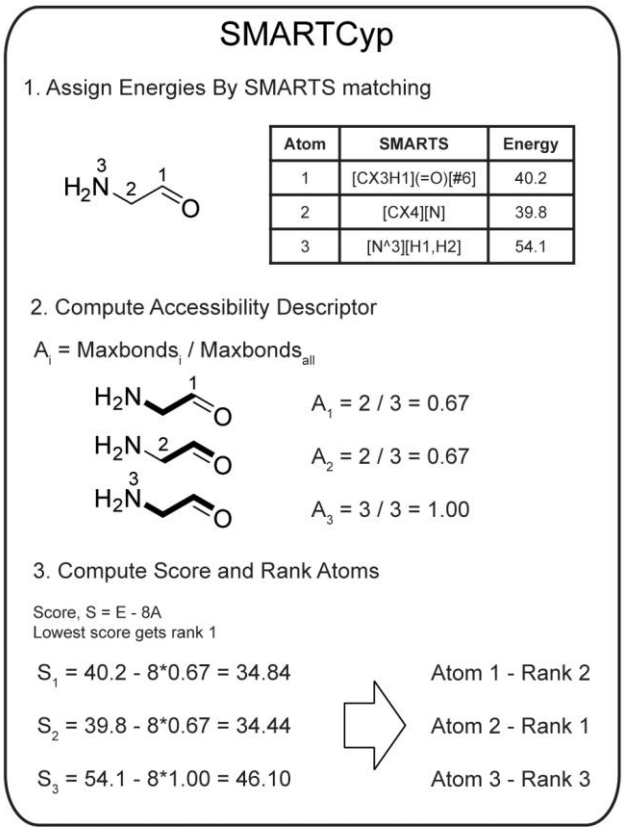
Prediction of Cytochrome P450 mediated metabolism. (ca. 90% of Phase I metabolism)

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

Model Building



Software execution



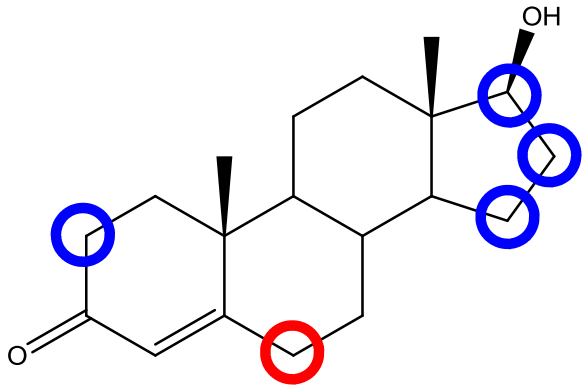
MetaPrint2D basics:

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

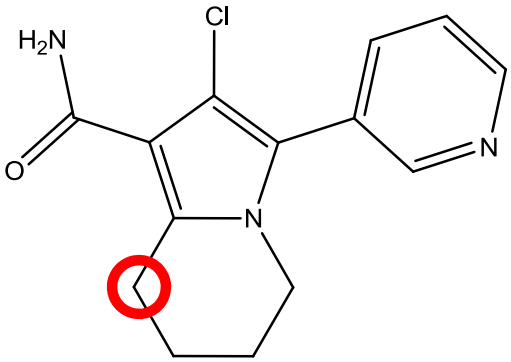
Examples with excellent SMARTCyp predictions

Major metabolites in red, and minor in blue.

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

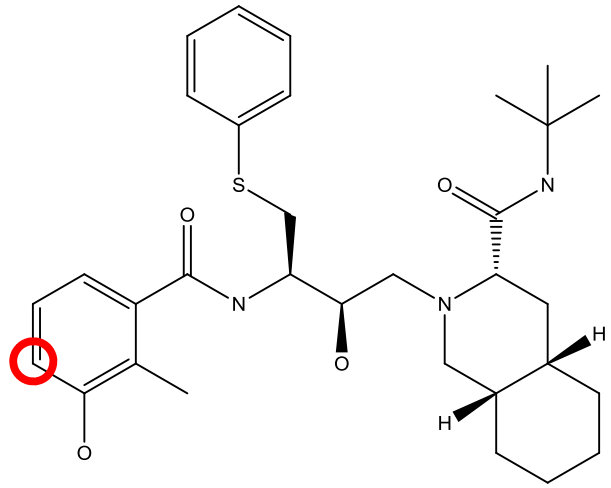


CMV342
C1CCN2C(=C(C(=C2C3=CN=CC=C3)Cl)C(=O)N)C1

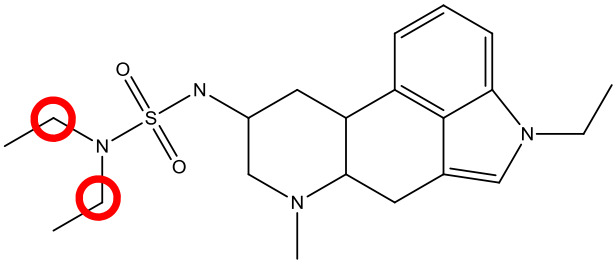


Examples with bad SMARTCyp predictions

Nelfinavir
CC1=C(C=CC=C1O)C(=O)NC(CSC2=CC=CC=C2)C(CN3C
C4CCCCC4CC3C(=O)NC(C)(C)C)O



CQA 206-291
CCN1C=C2CC3C(CC(CN3C)NS(=O)(=O)N(CC)CC)C4=C
2C1=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-4aminoazobenzene: COC1=C(C=CC(=C1)N=NC2=CC=CC=C2)N
Aflatoxin B_1: 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
benz0[a]anthracene: c34cc2ccc1ccccc1c2cc3cccc4