



Prediction of Cytochrome P450 Mediated Metabolism

Patrik Rydberg

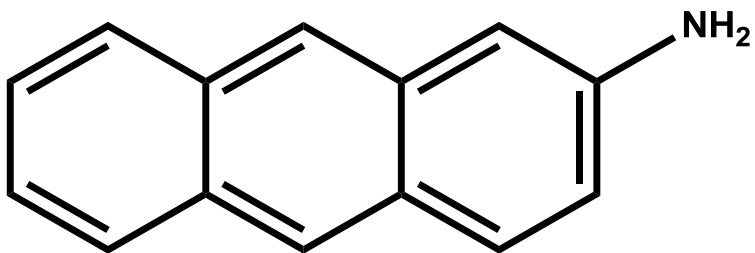
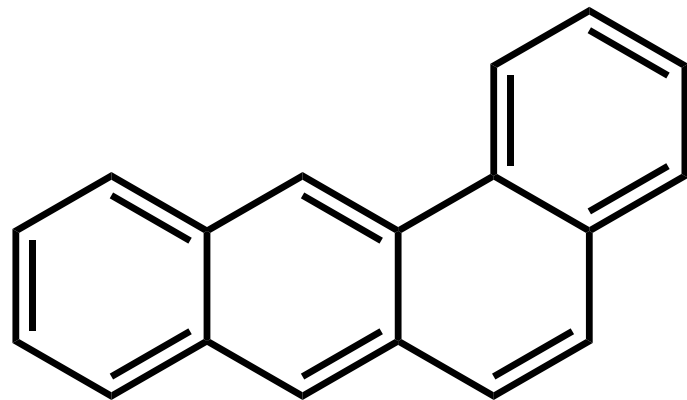
Ph.D., Associate Professor
Department of Medicinal Chemistry
University of Copenhagen



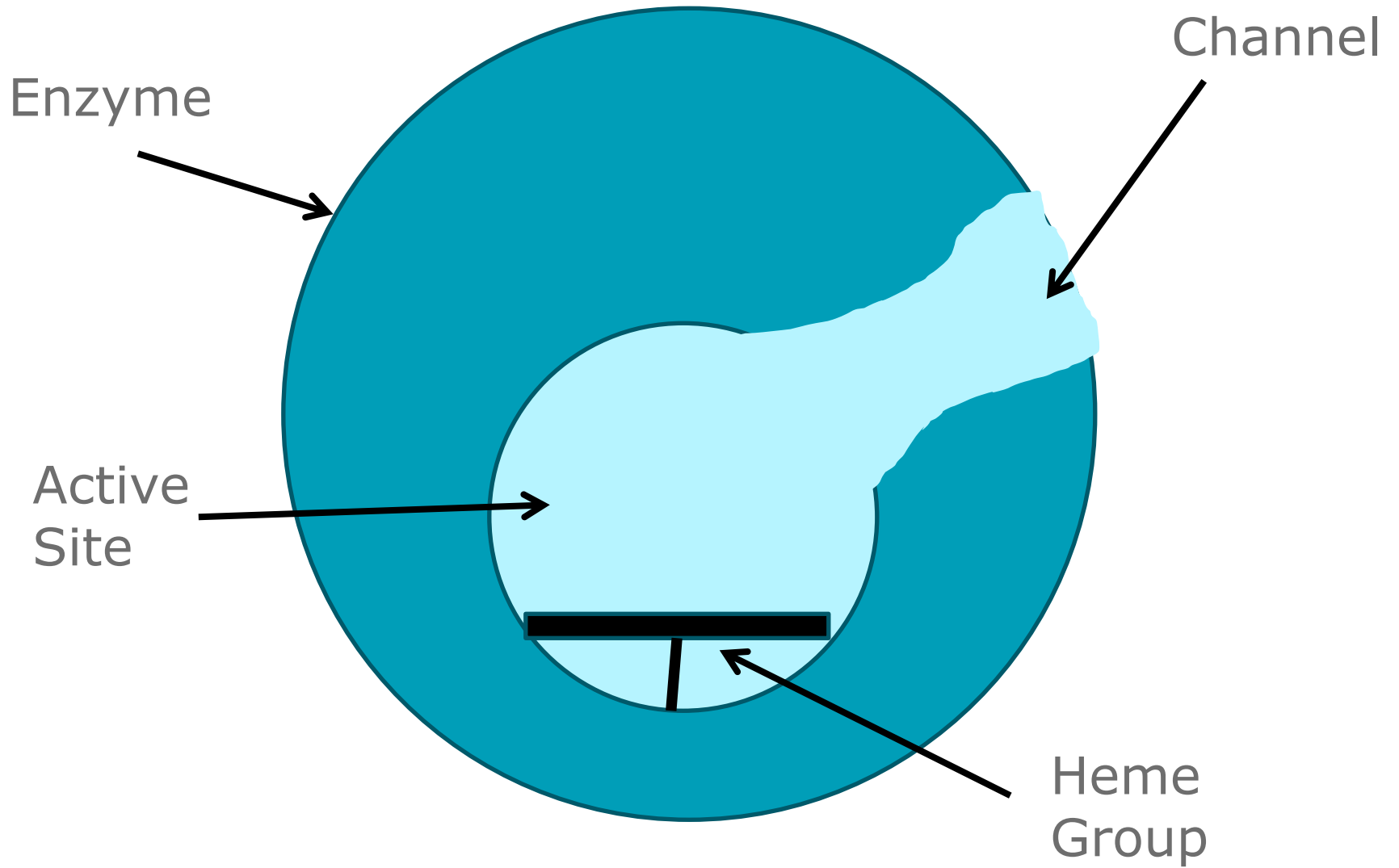
90% of Drugs
are metabolized by P450s

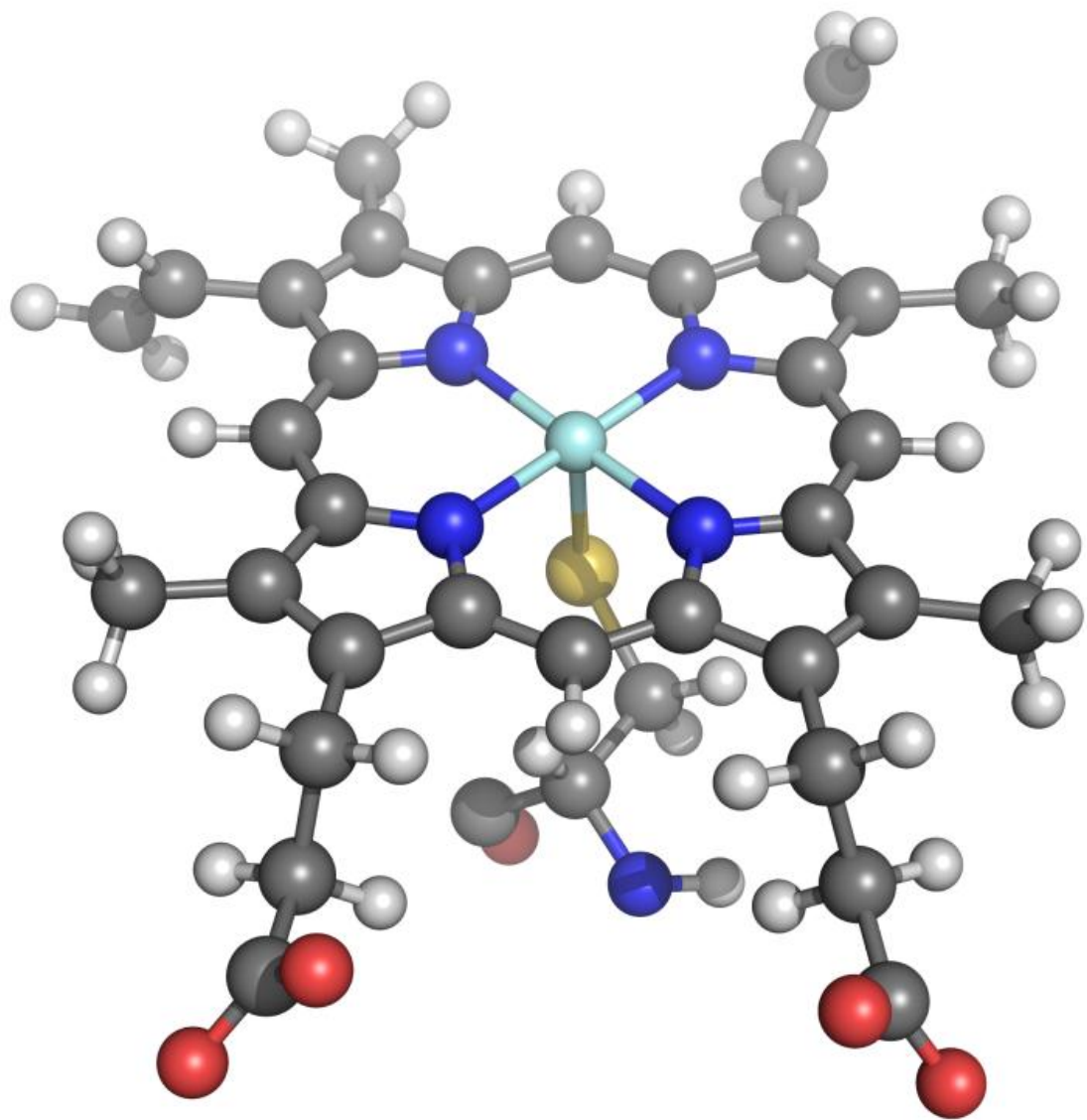


Creates toxicity

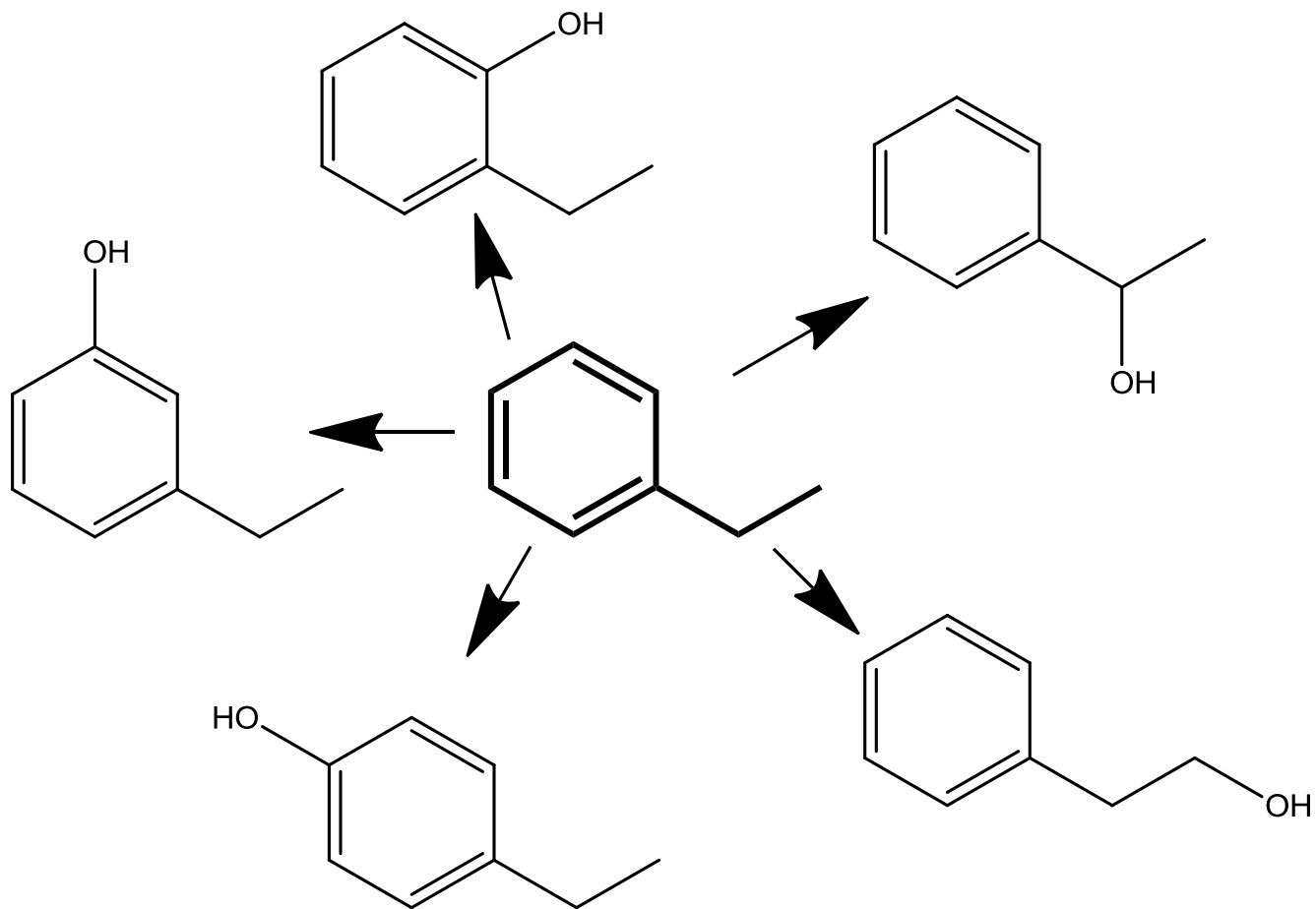




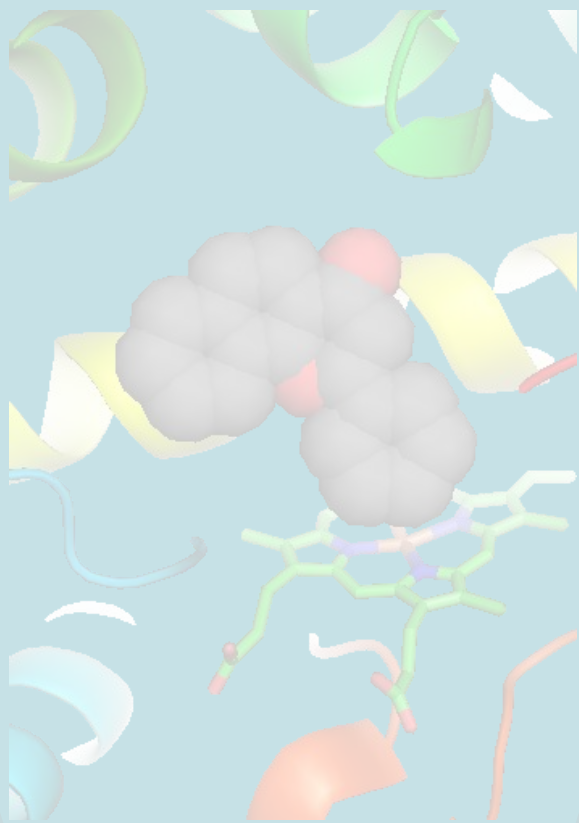




?



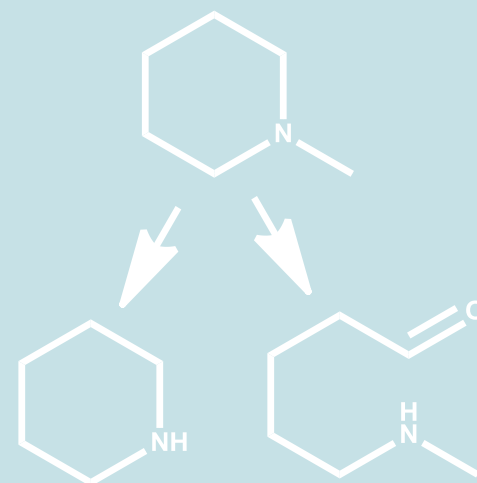
Binding



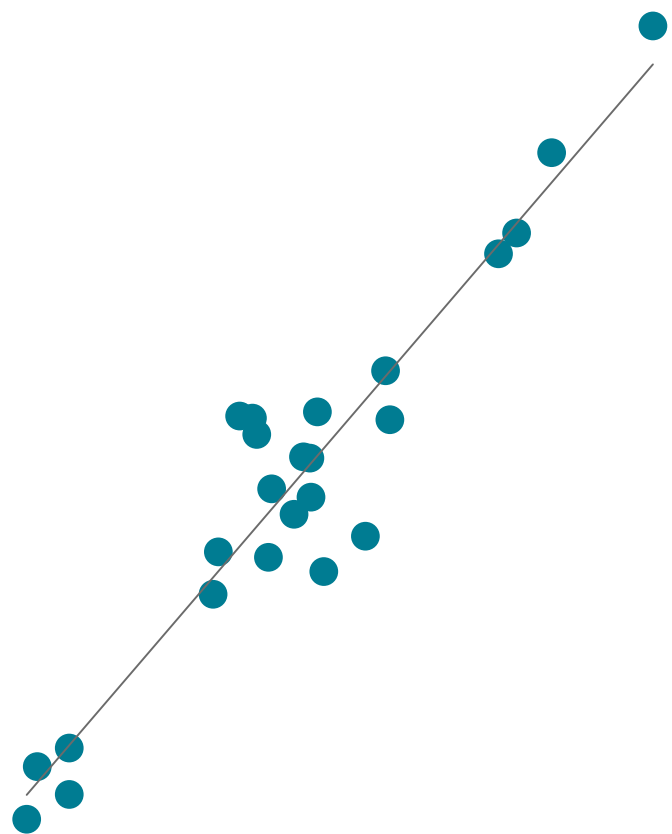
Reactivity



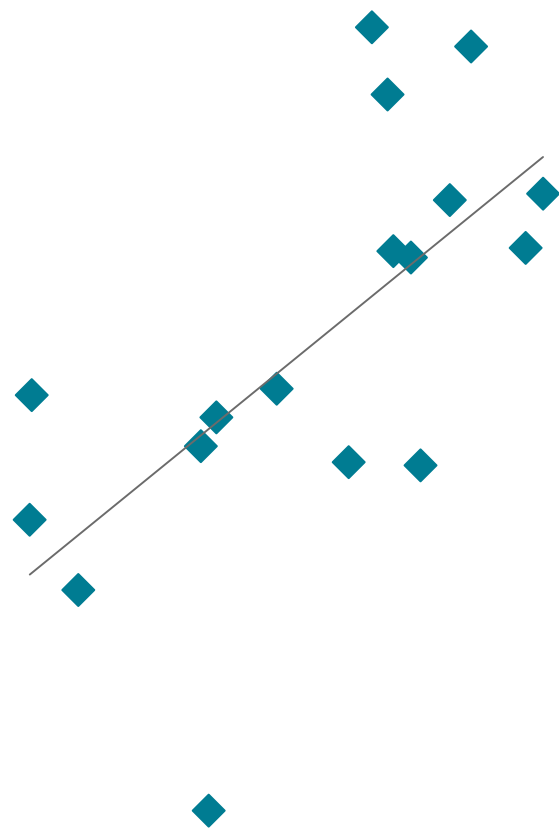
Entropy



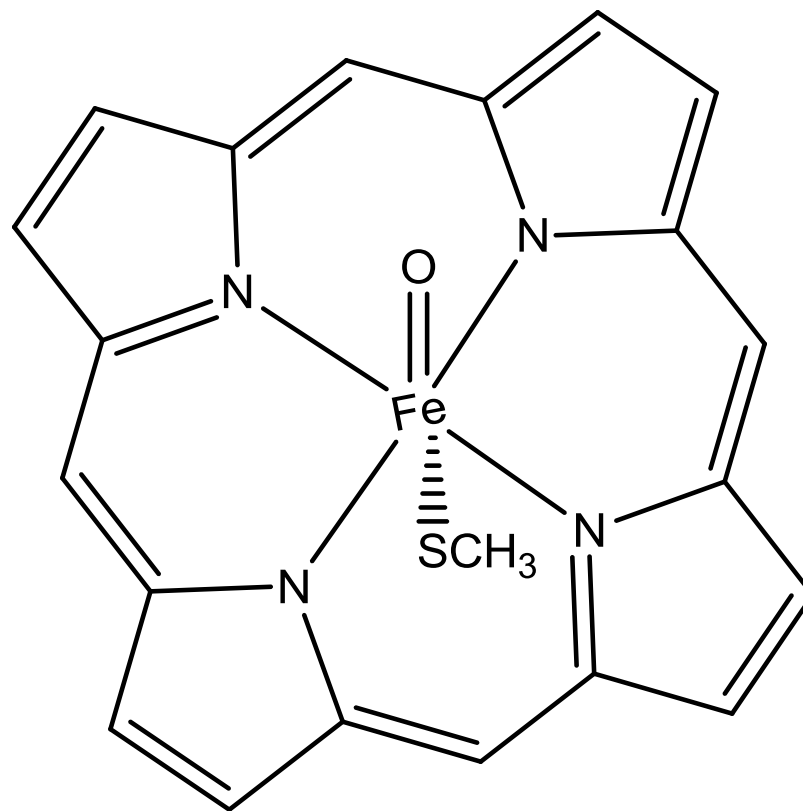
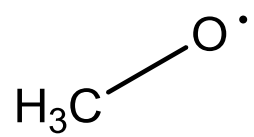
Semi-empirical data is very model unreliable



Aliphatic carbons

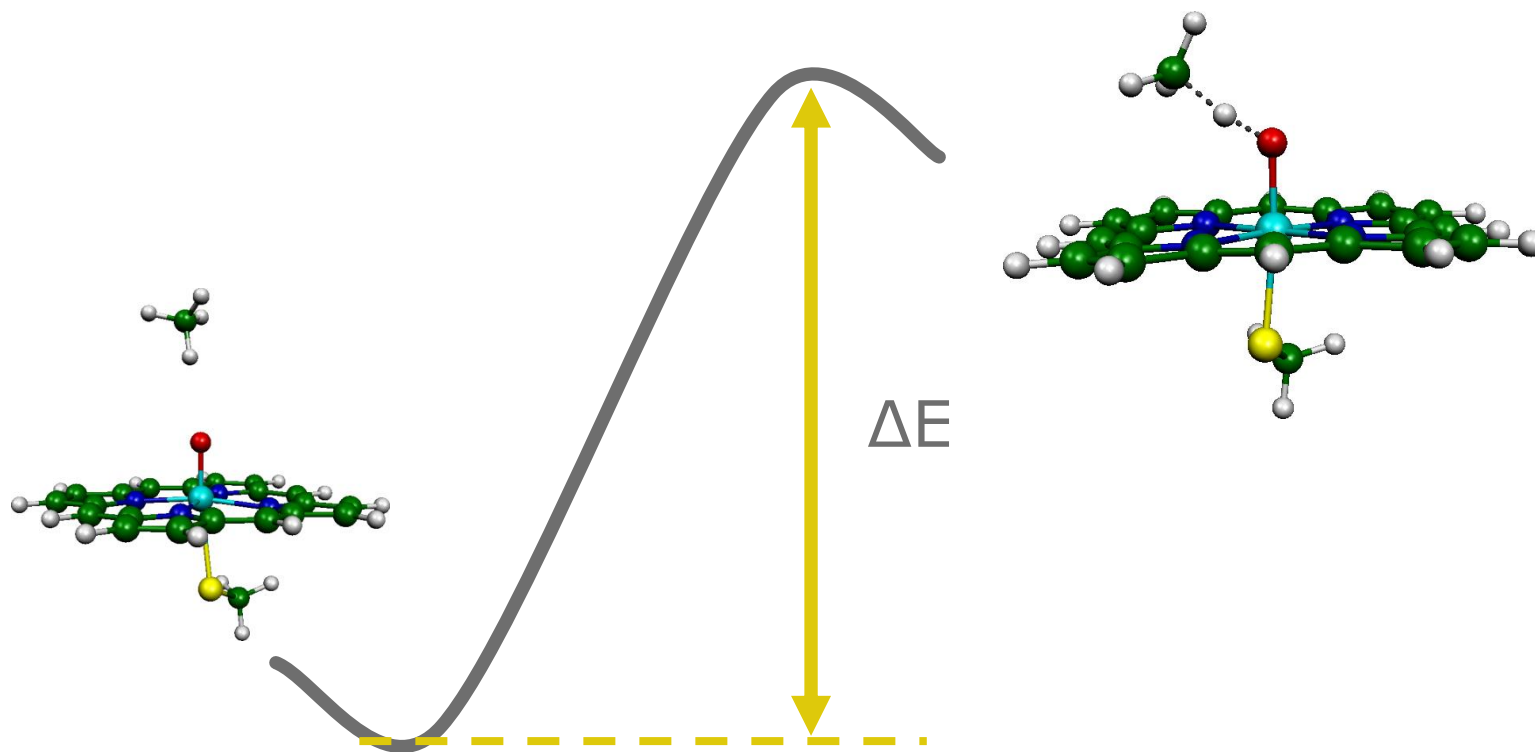


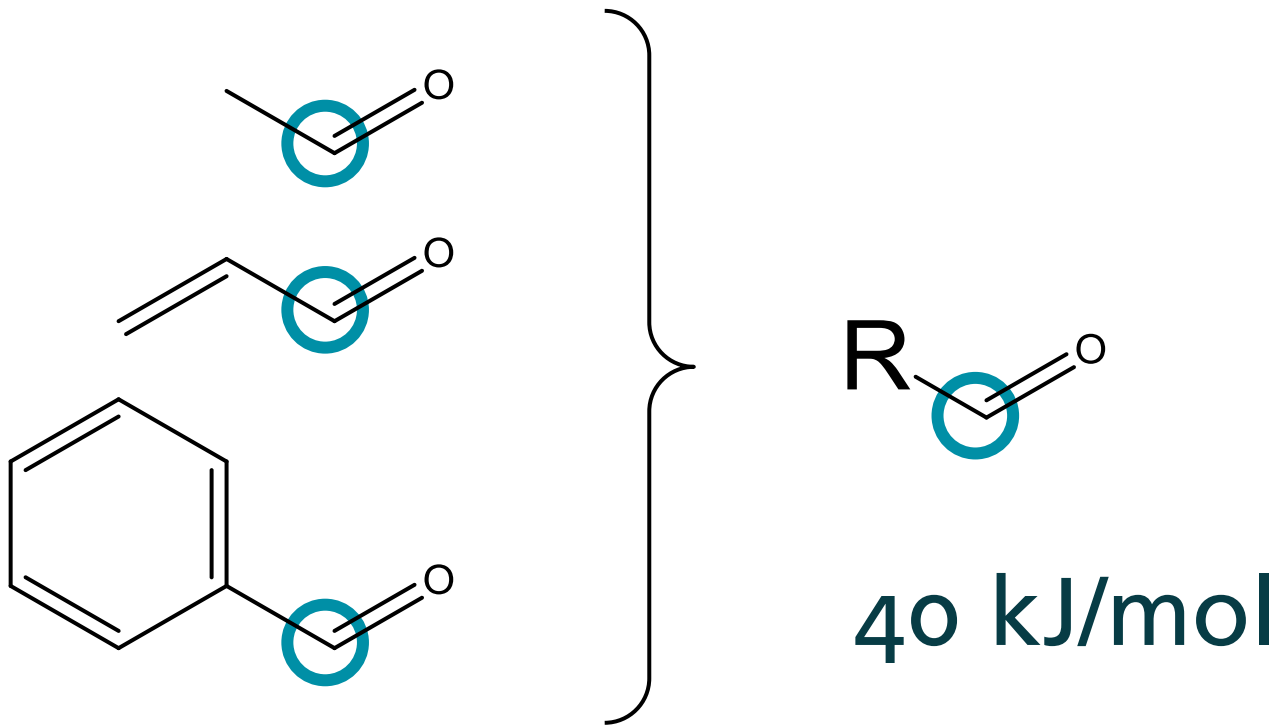
Aromatic carbons

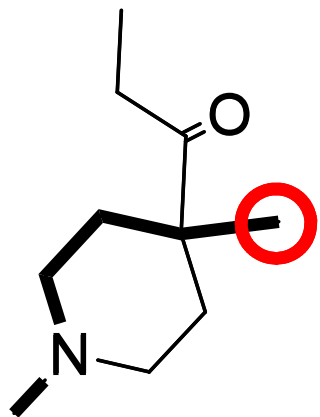


200+ Transition States

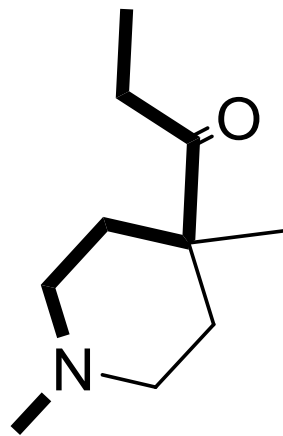
All major reaction types







Maxbonds_i = 5



Maxbonds_{all} = 7

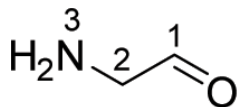
Accessibility = $5/7 = 0.7$

SMARTCyp

$$\text{Score} = \text{Energy} - 8 * \text{Accessibility}$$

SMARTCyp

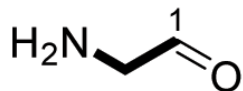
1. Assign Energies By SMARTS matching



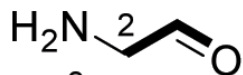
Atom	SMARTS	Energy
1	[CX3H1](=O)[#6]	40.2
2	[CX4][N]	39.8
3	[N^3][H1,H2]	54.1

2. Compute Accessibility Descriptor

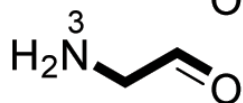
$$A_i = \text{Maxbonds}_i / \text{Maxbonds}_{\text{all}}$$



$$A_1 = 2 / 3 = 0.67$$



$$A_2 = 2 / 3 = 0.67$$



$$A_3 = 3 / 3 = 1.00$$

3. Compute Score and Rank Atoms

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

Lowest score gets rank 1

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

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

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

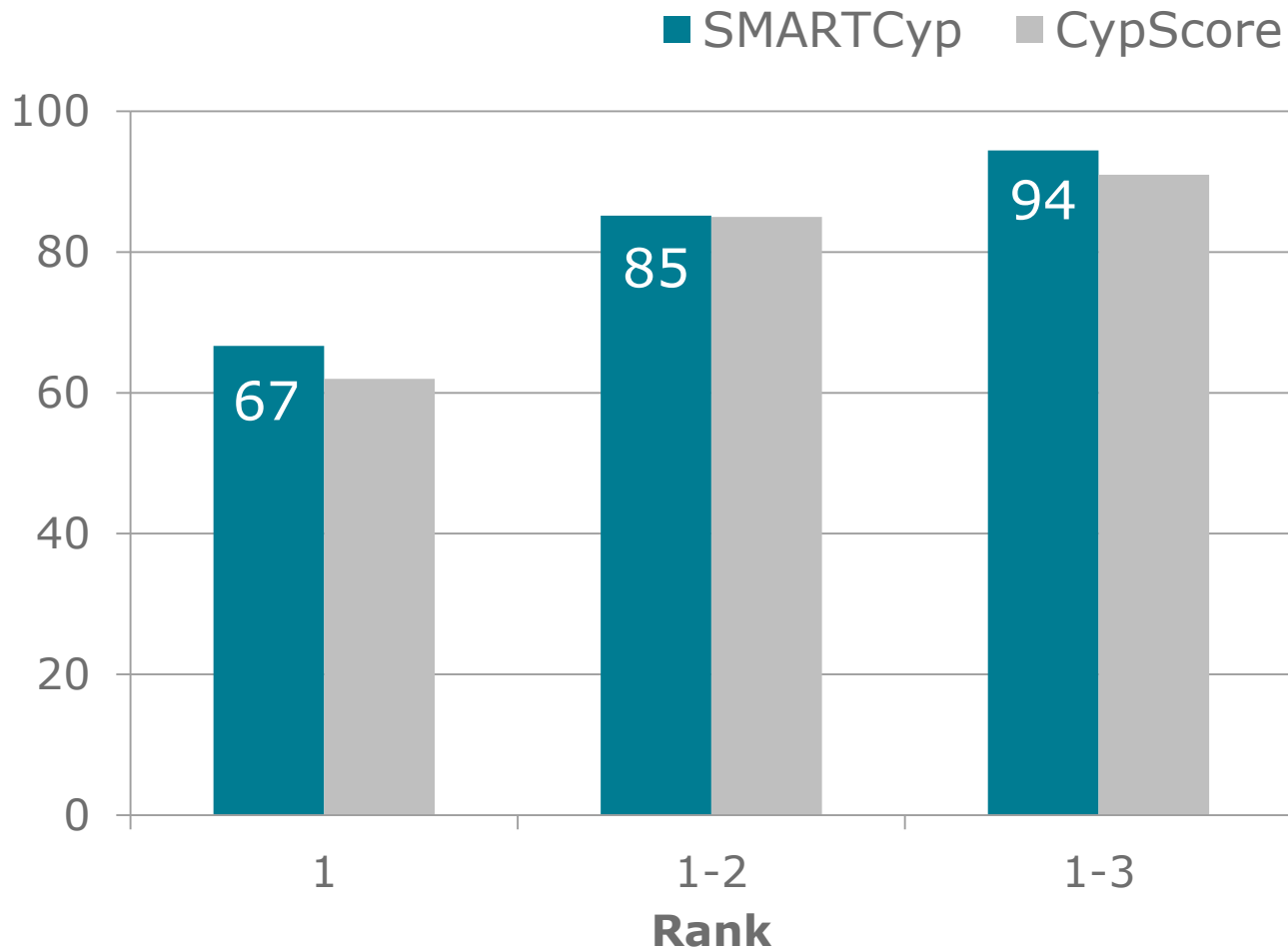


Atom 1 - Rank 2

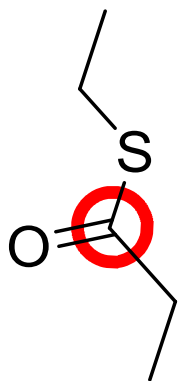
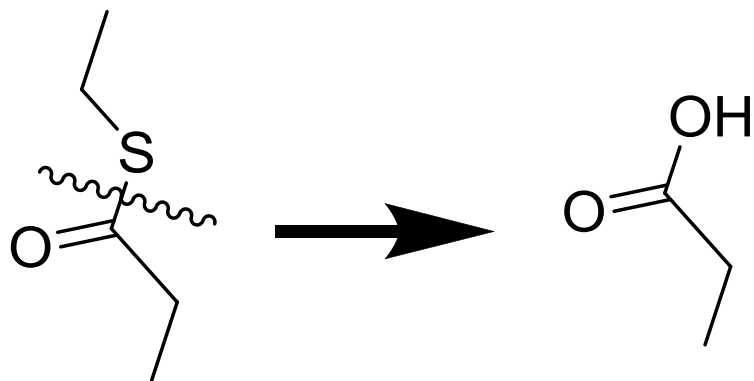
Atom 2 - Rank 1

Atom 3 - Rank 3

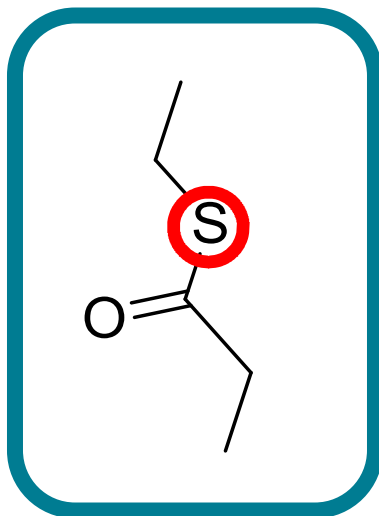
Isoform Unspecific Metabolism



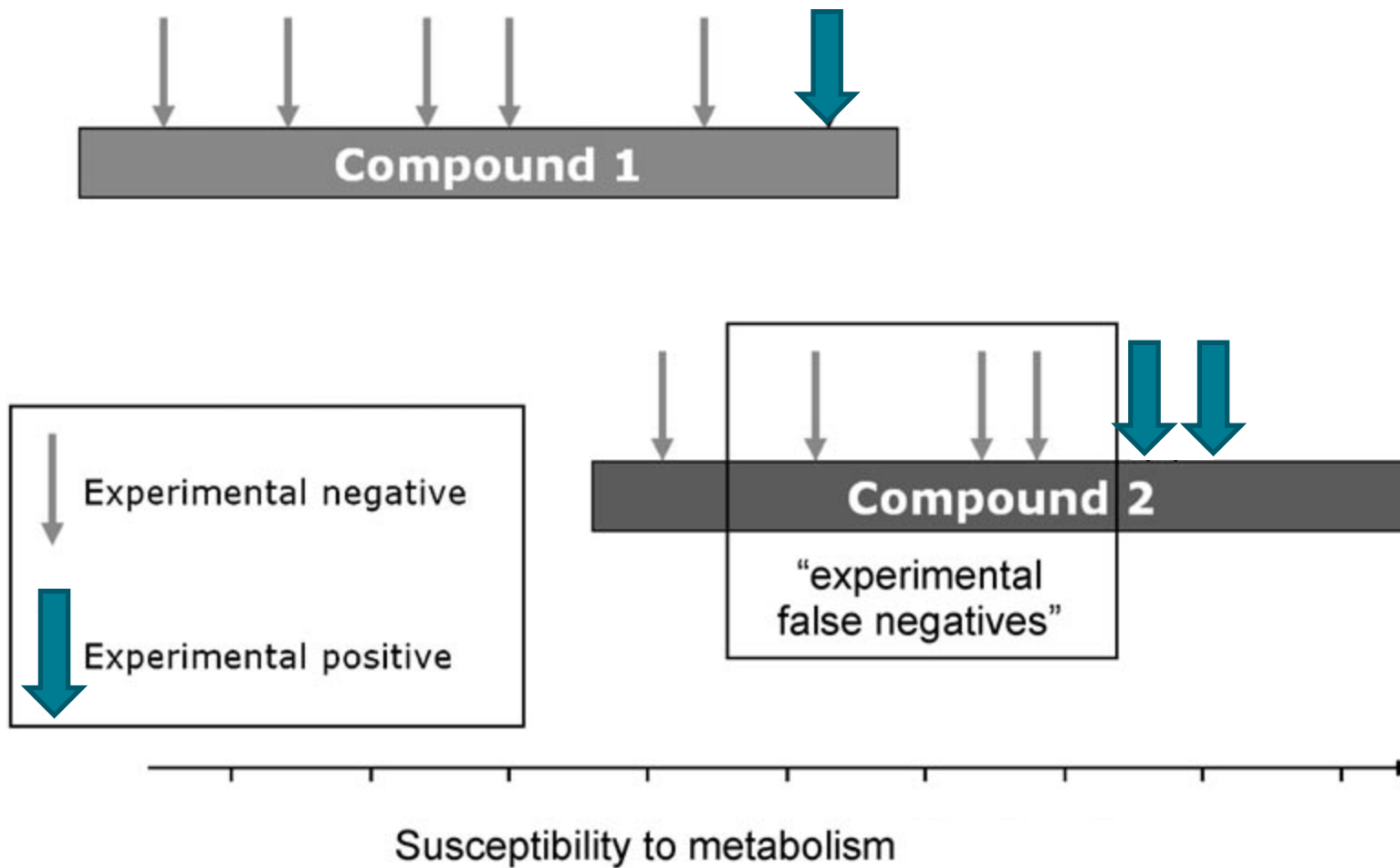
Database Problems



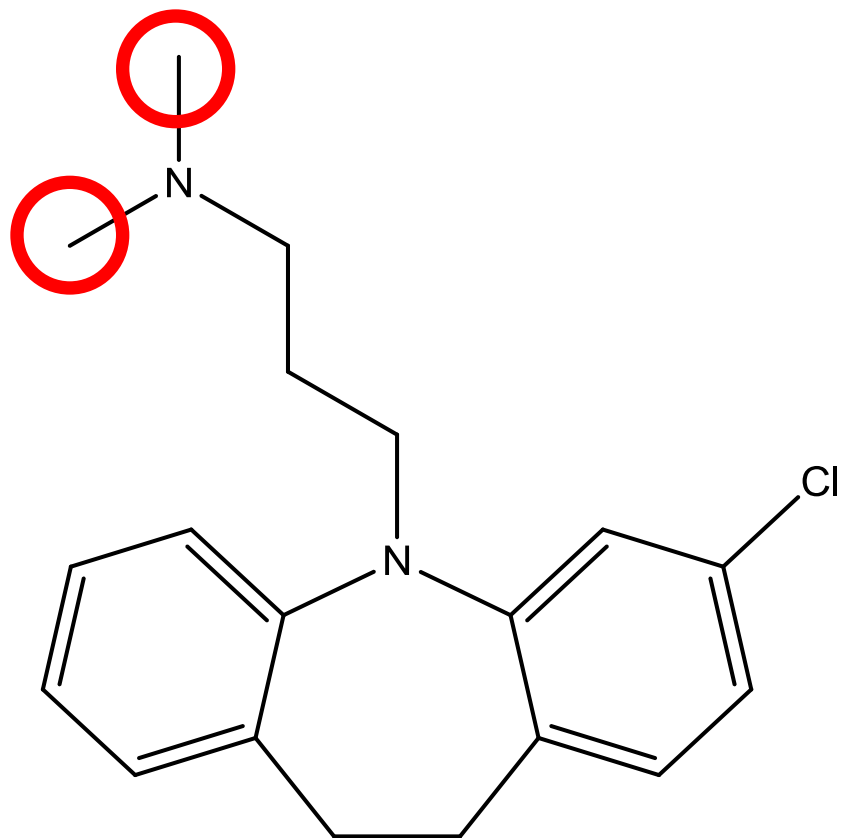
OR



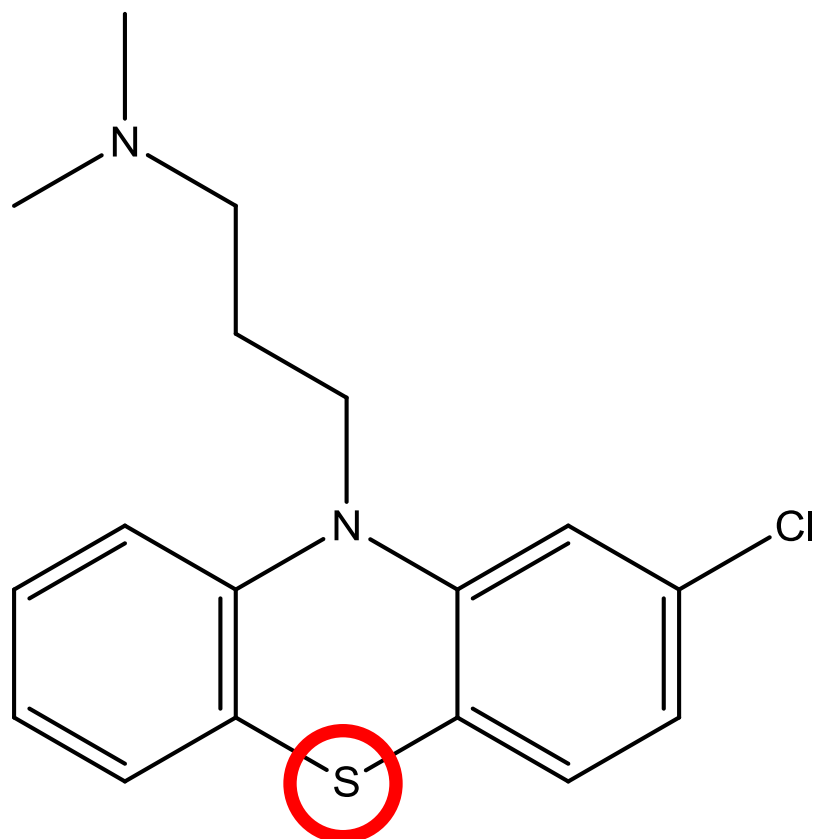
False negatives



False negatives – N-dealkylation

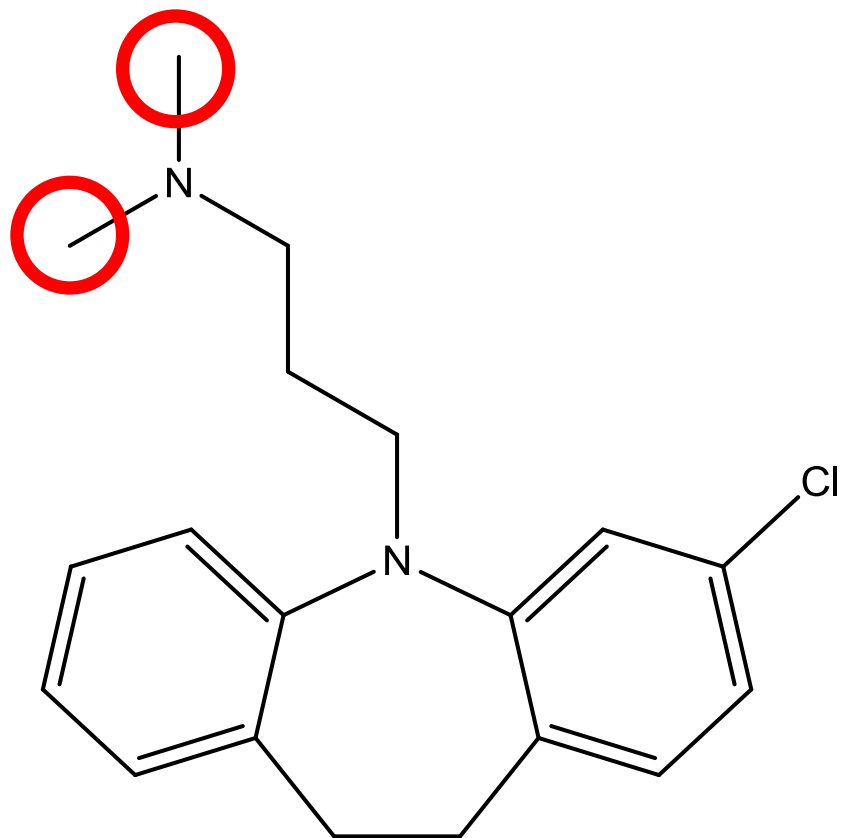


Clomipramine

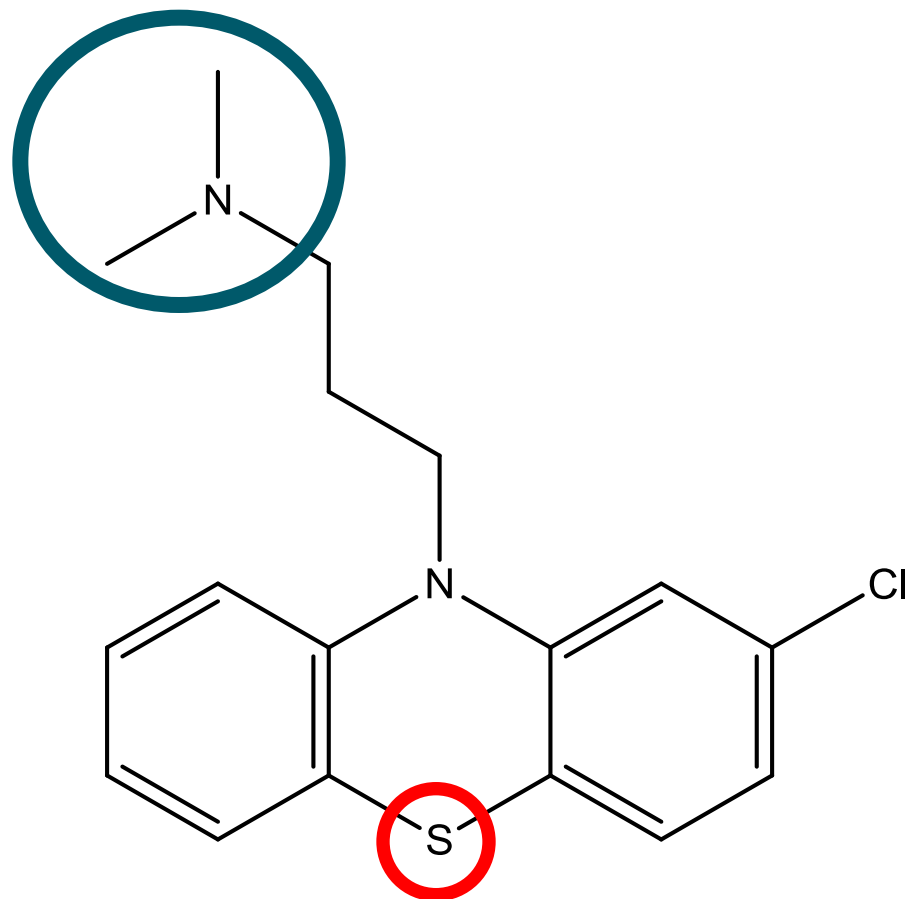


Chlorpromazine

False negatives – N-dealkylation

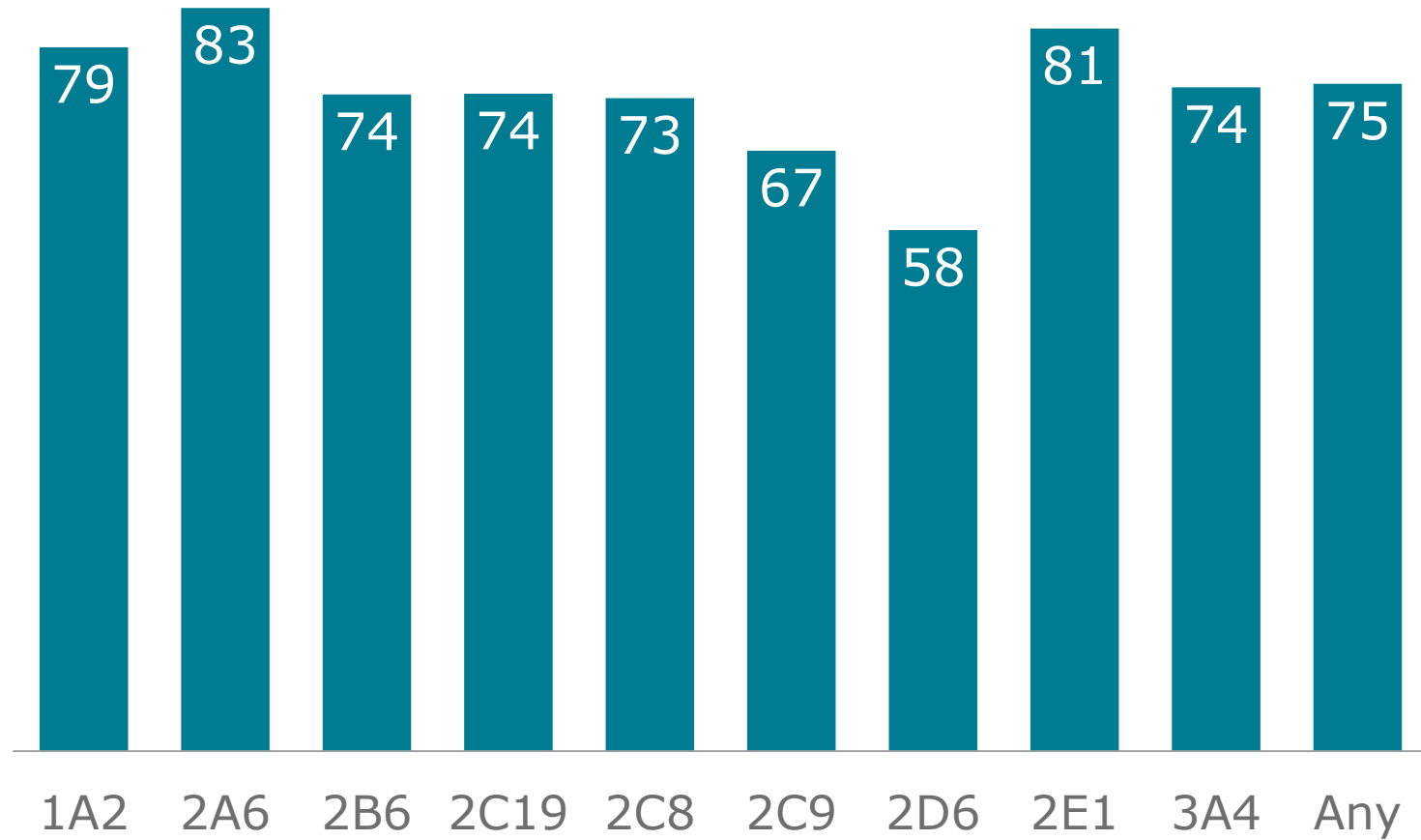


Clomipramine

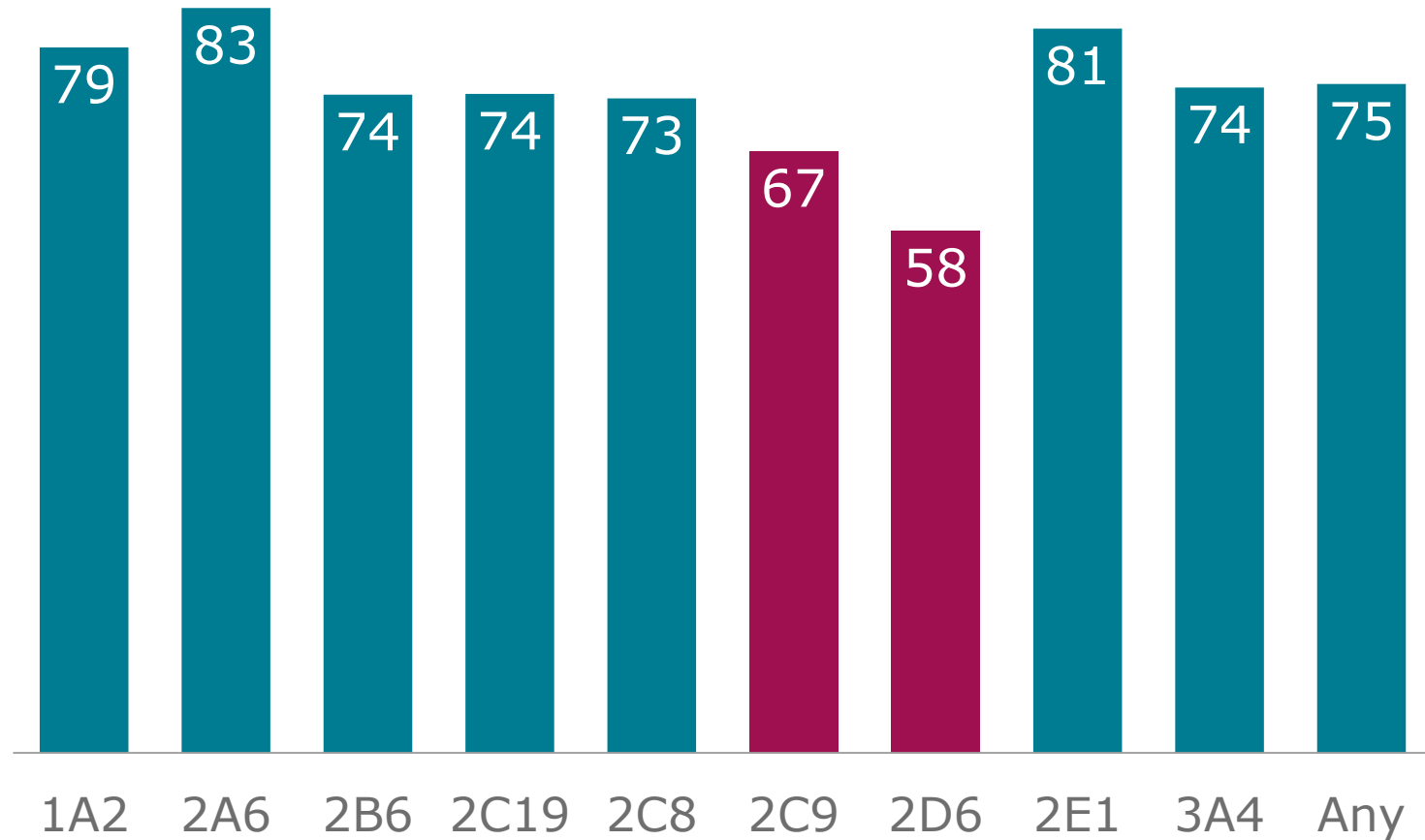


Chlorpromazine

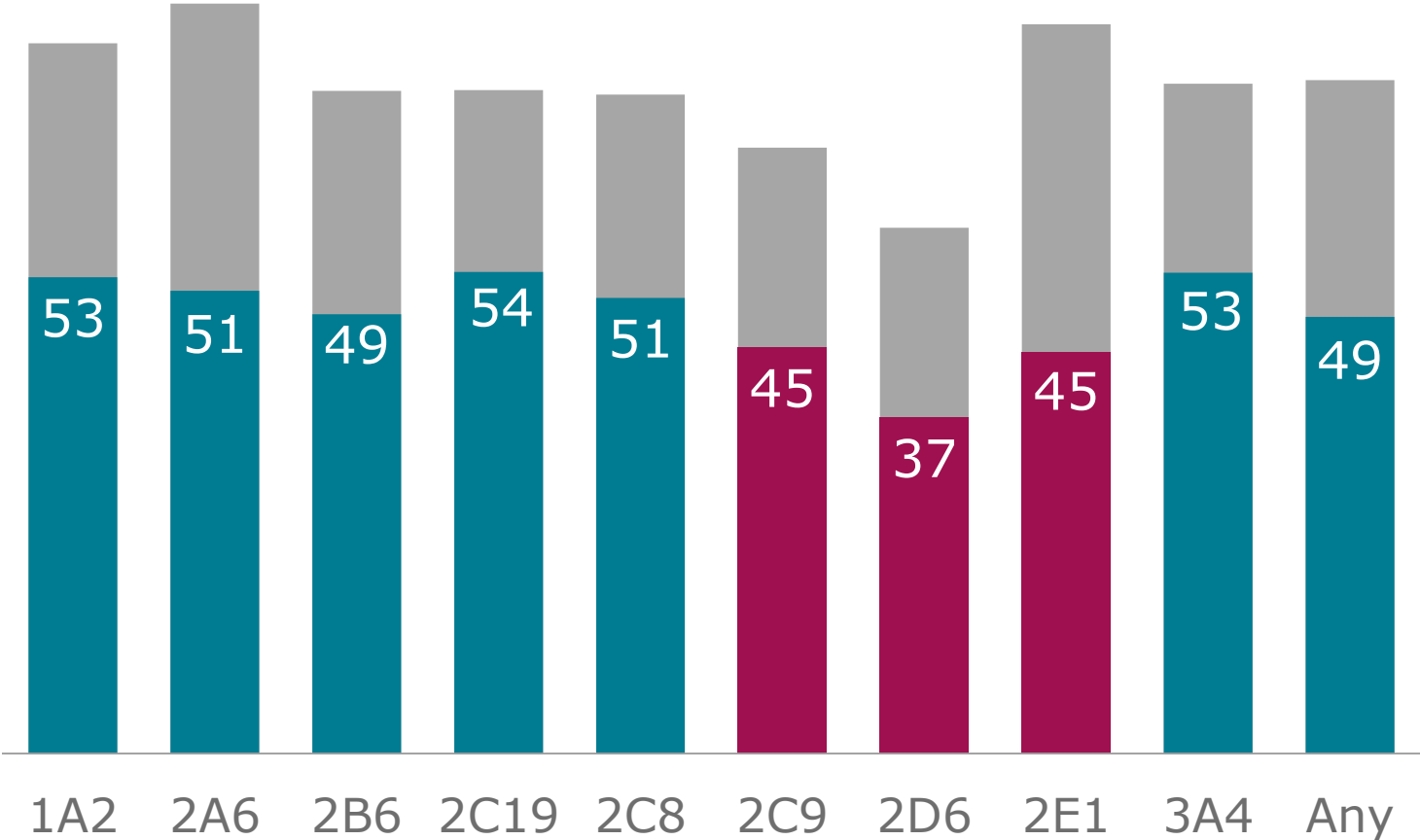
SMARTCyp Accuracy for Nine Isoforms



SMARTCyp Accuracy for Nine Isoforms



Enrichment



www.farma.ku.dk/smartcyp/

SMARTCyp Start

About

Background

Download

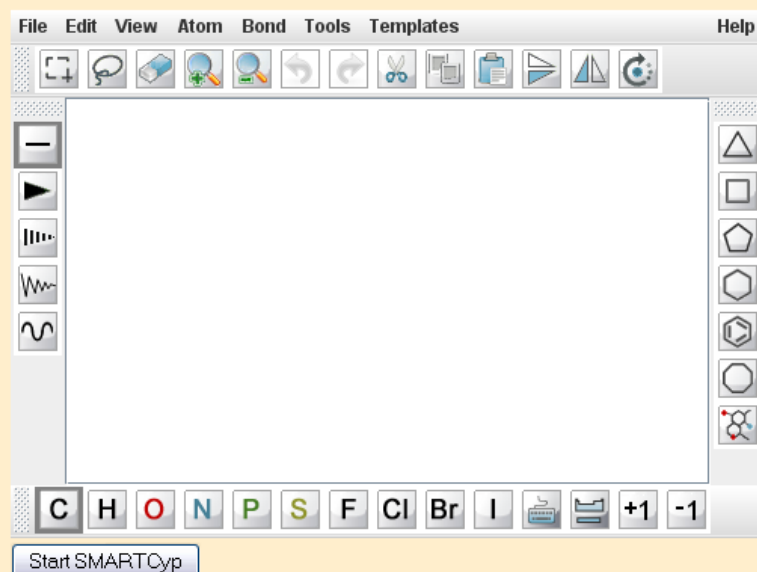
Help

SMARTCyp Web Service

SMARTCyp predicts the sites in molecules that are most liable to cytochrome P450 mediated metabolism.

You have 3 options for creating/importing molecules:

Draw your molecule



The screenshot shows a web-based chemical drawing application. At the top is a menu bar with 'File', 'Edit', 'View', 'Atom', 'Bond', 'Tools', 'Templates', and 'Help'. Below the menu is a toolbar with various drawing tools like lines, polygons, and rings. The main area is a large white canvas for drawing. On the left side of the canvas are vertical toolbars for bond types and atom types. At the bottom, there is a row of buttons for selecting atoms: C, H, O, N, P, S, F, Cl, Br, I, and a '+1' and '-1' button. A 'Start SMARTCyp' button is located at the bottom left of the drawing area.

Upload a file ?

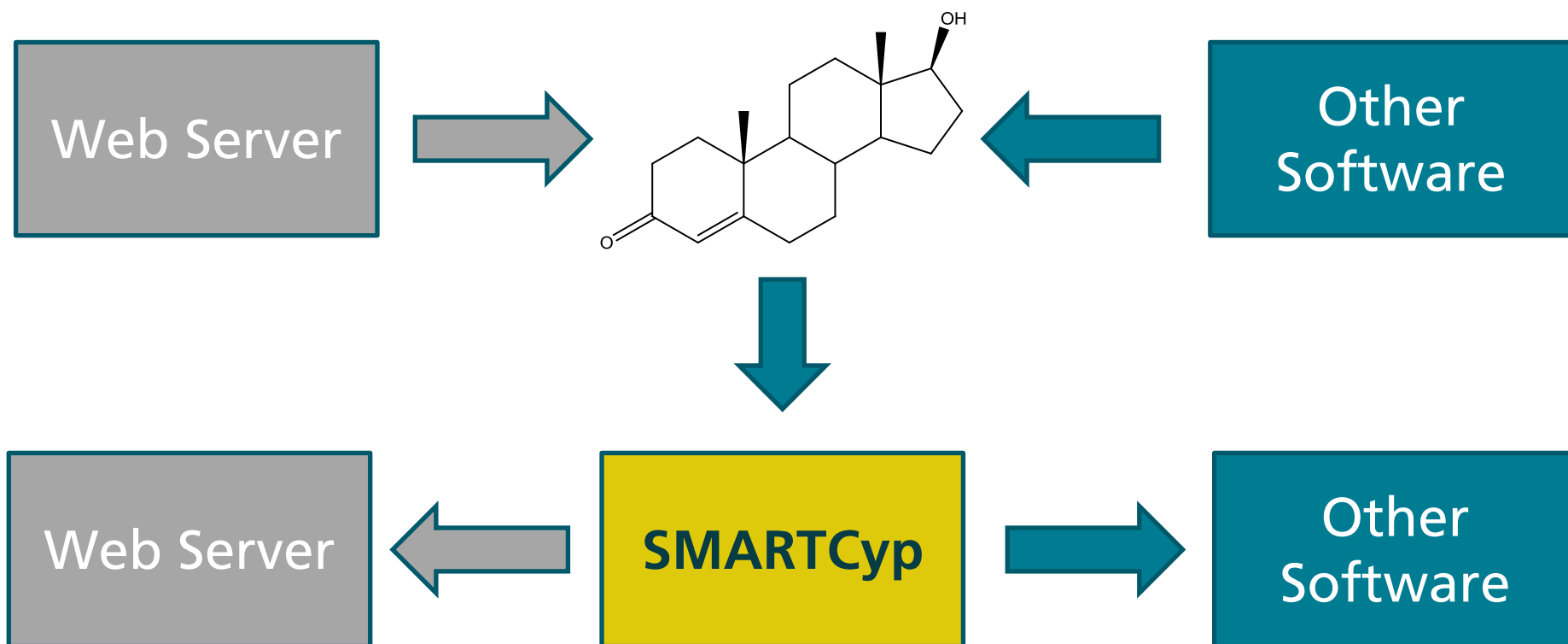
Bläddra...

Start SMARTCyp

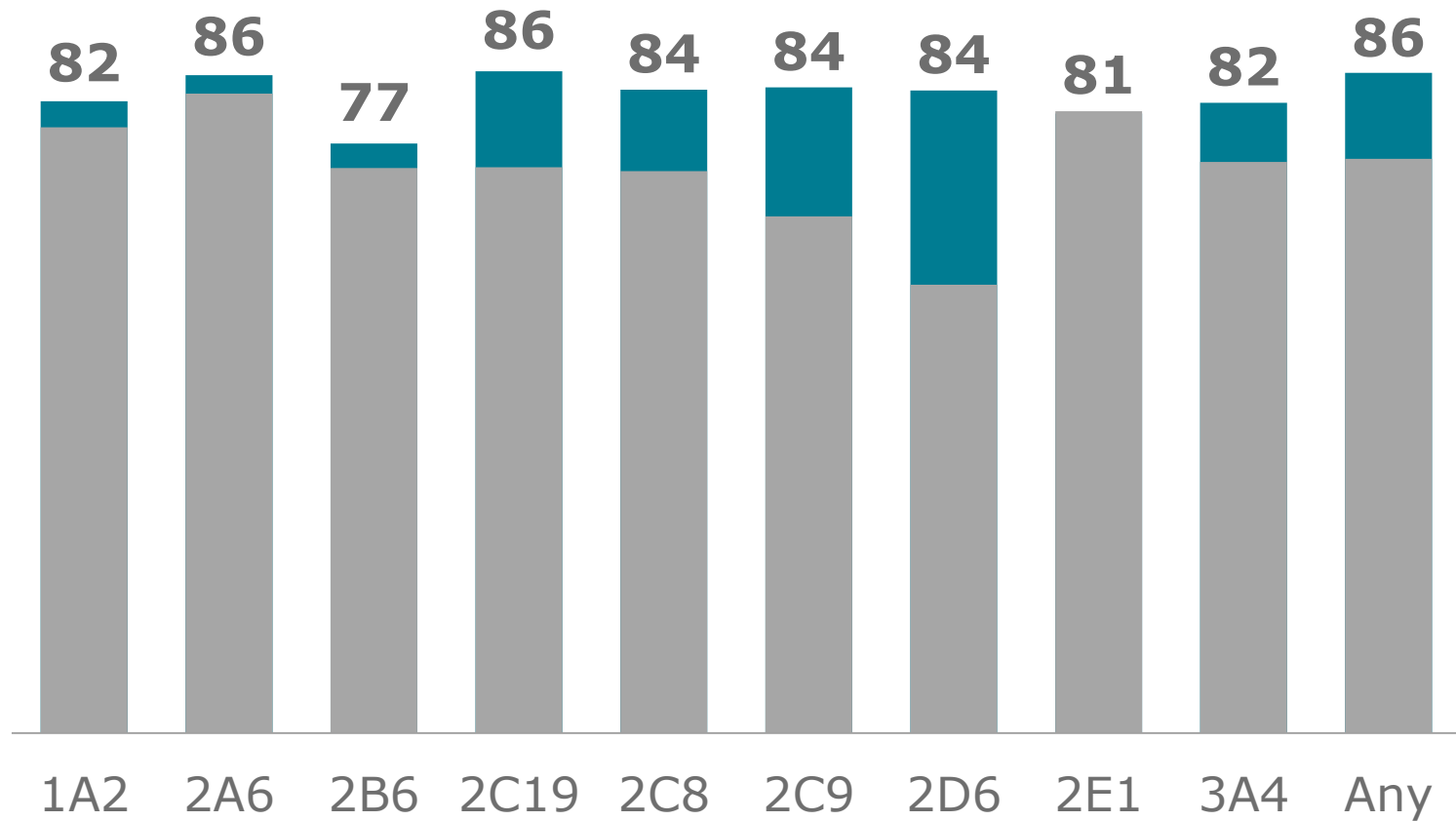
Enter SMILES strings

Start SMARTCyp

SMARTCyp is Flexible

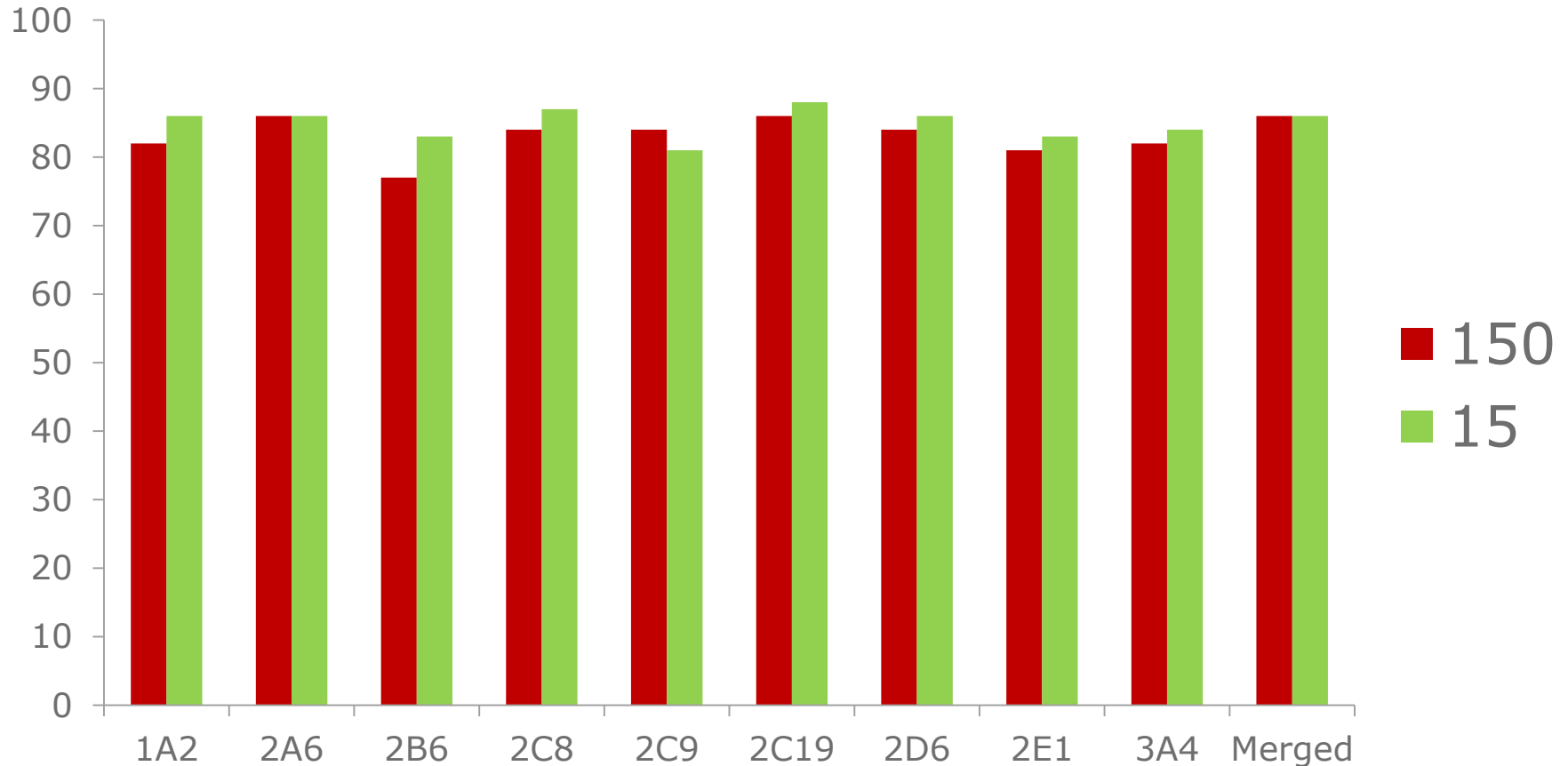


SMARTCyp Extended with RS-Predictor



The Next Step: Sensible Atomic Descriptors

15 vs. 150 descriptors



Metabolite prediction in ToxTree 2.5

<http://toxtree.sourceforge.net/>

Usage and Availability

www.farma.ku.dk/smartcyp

ToxTree

MOE

Pipeline Pilot

Bioclipse

METEOR



What do we need?

What does the future hold?

Better and more understandable models

More knowledge of P450 metabolism

for references
google "smartcyp"

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