Prediction of Cytochrome P450 Mediated Metabolism

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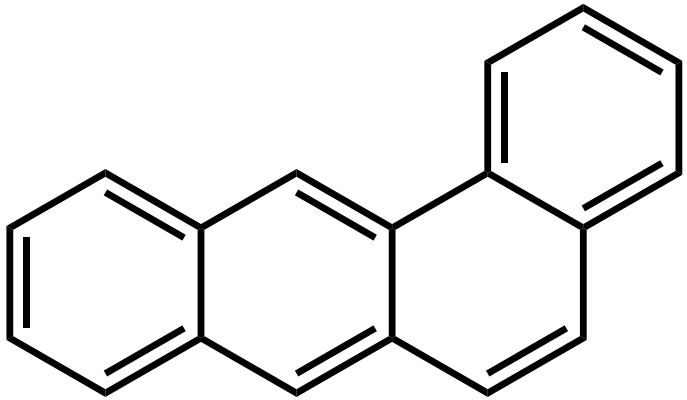
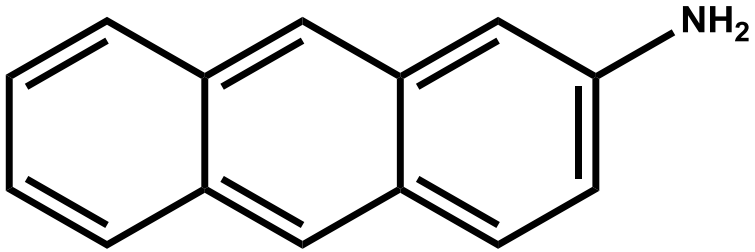
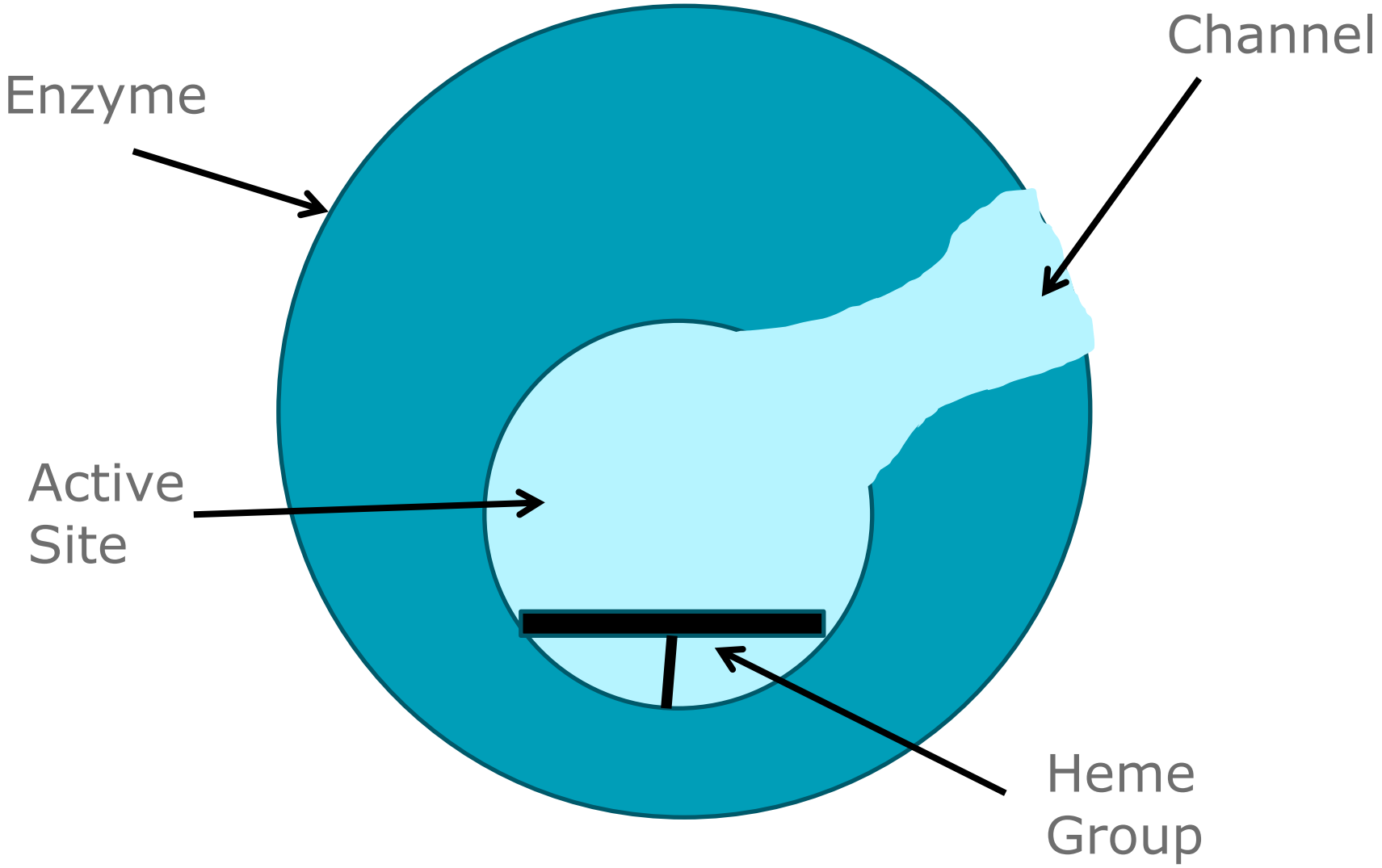
90% of Drugs

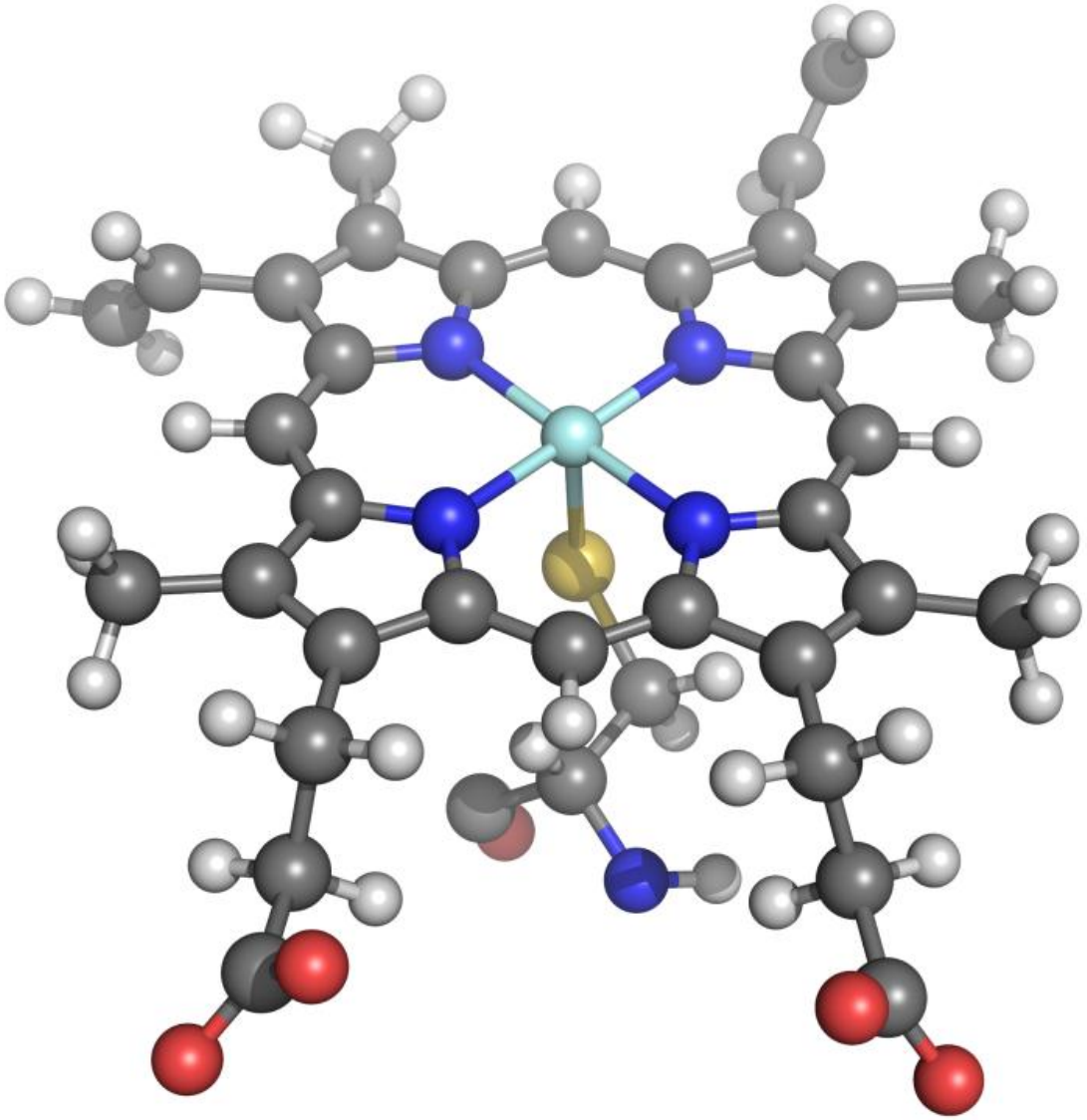
are metabolized by P450s

Creates toxicity

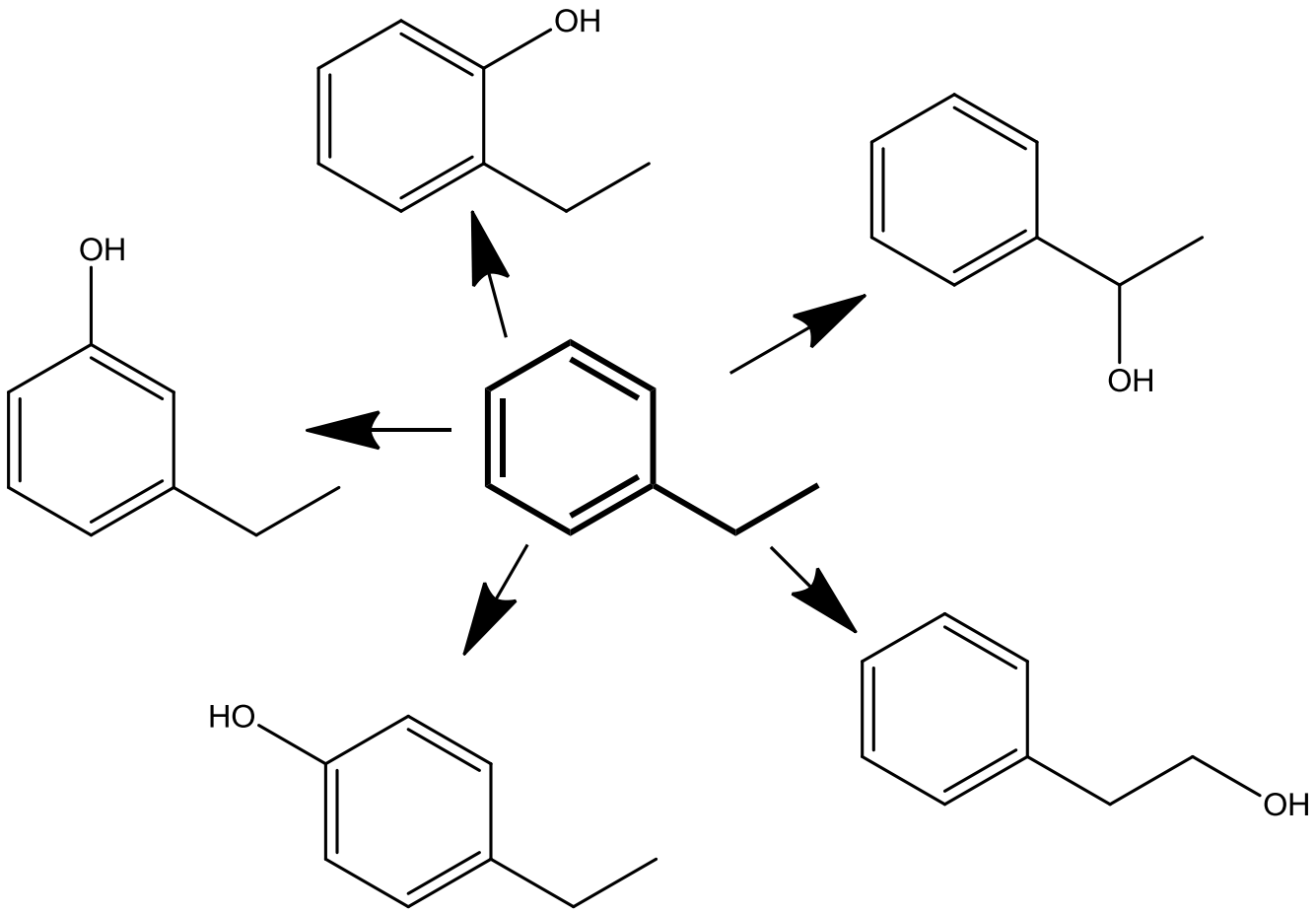





Enzyme
Channel
Active
Site
Heme
Group

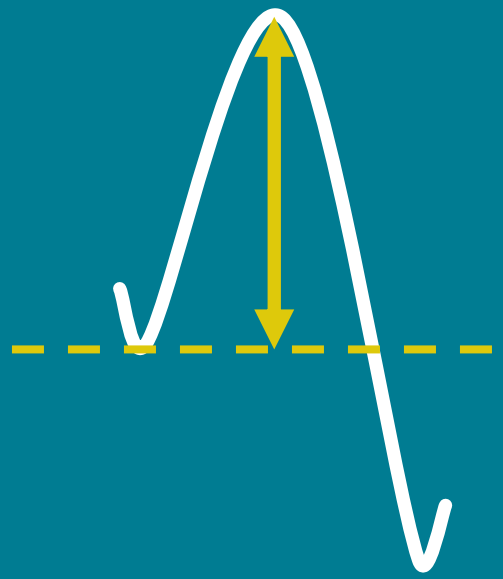


?


OH
OH
OH
HO
OH

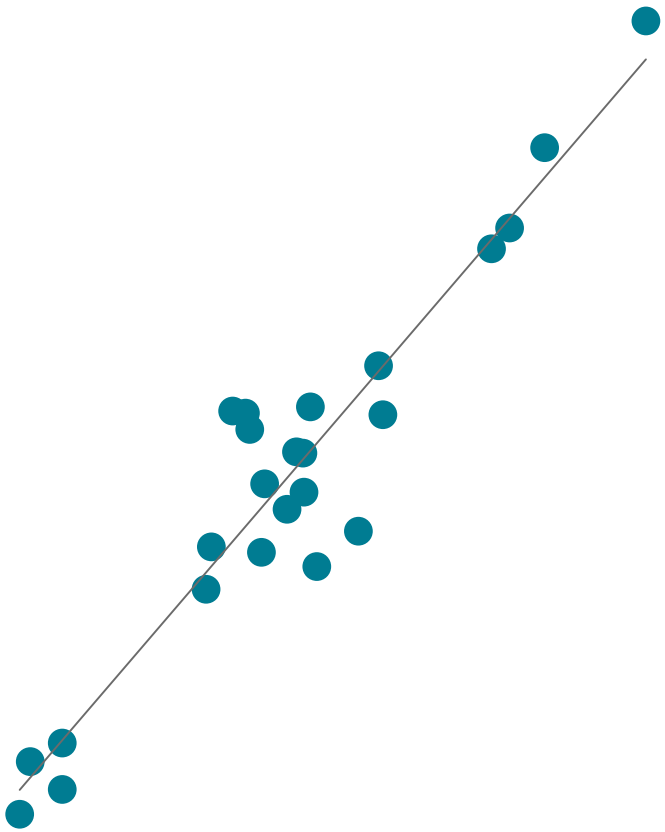
Binding

Reactivity

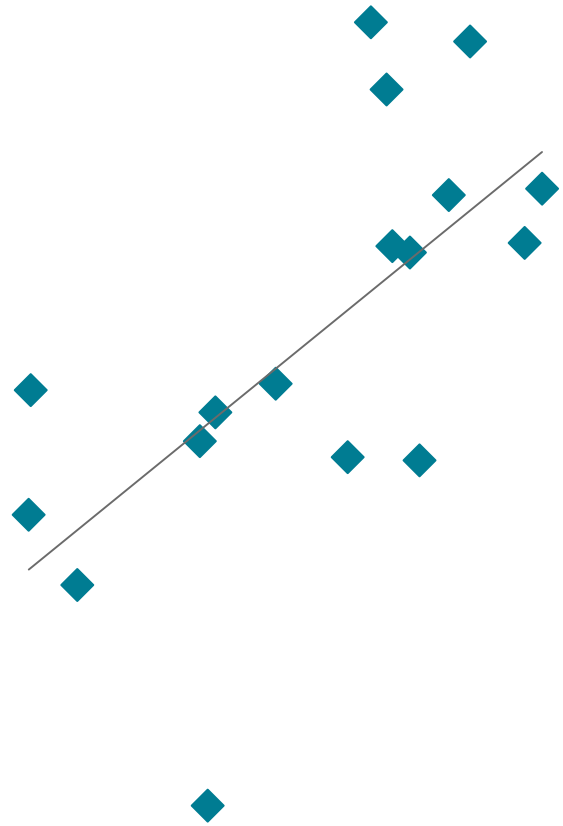


Entropy

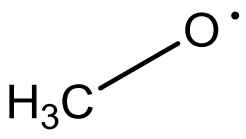
Semi-empirical methoxy model unreliable

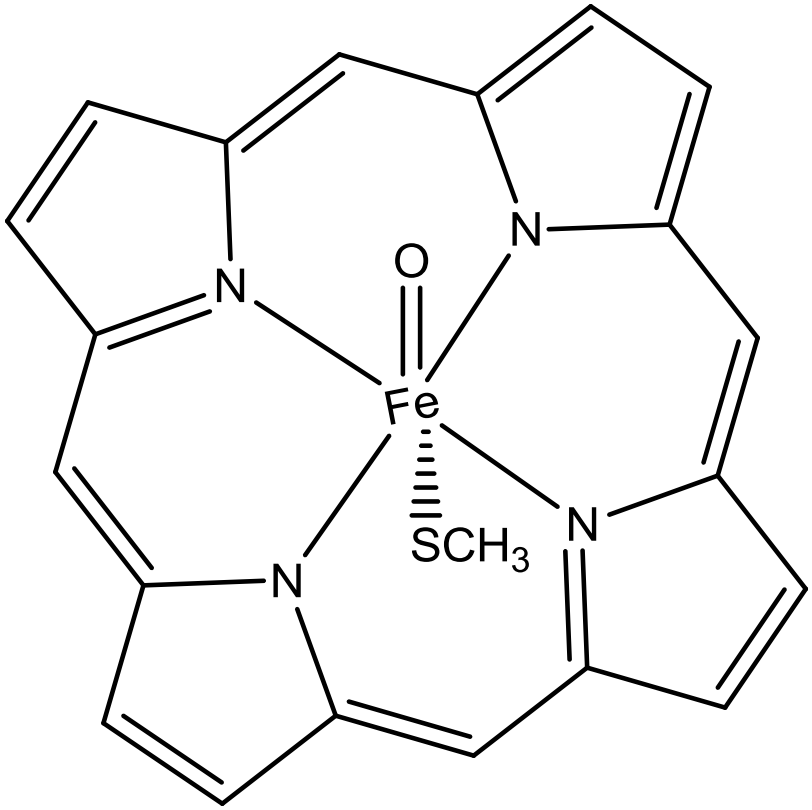


Aliphatic carbons



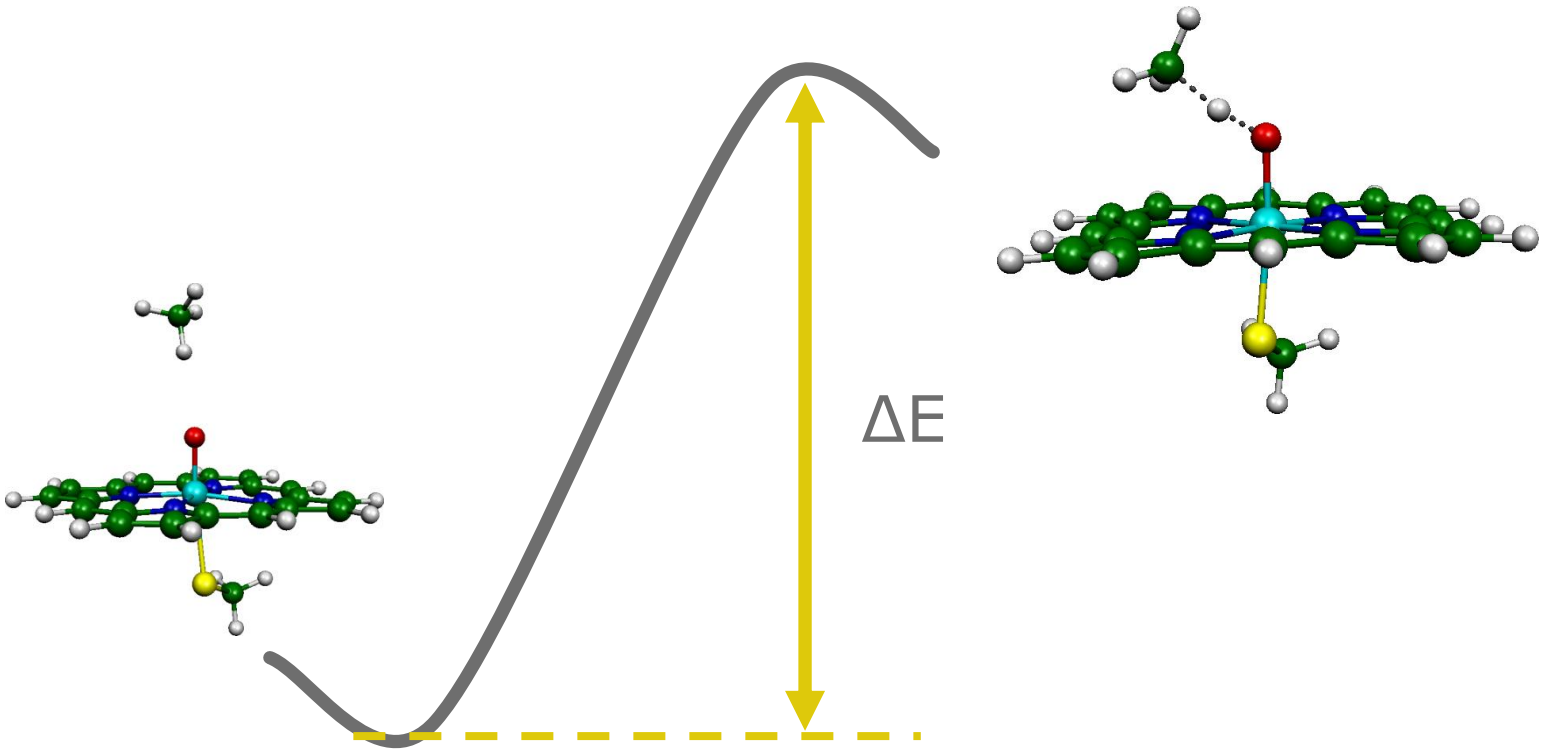
Aromatic carbons

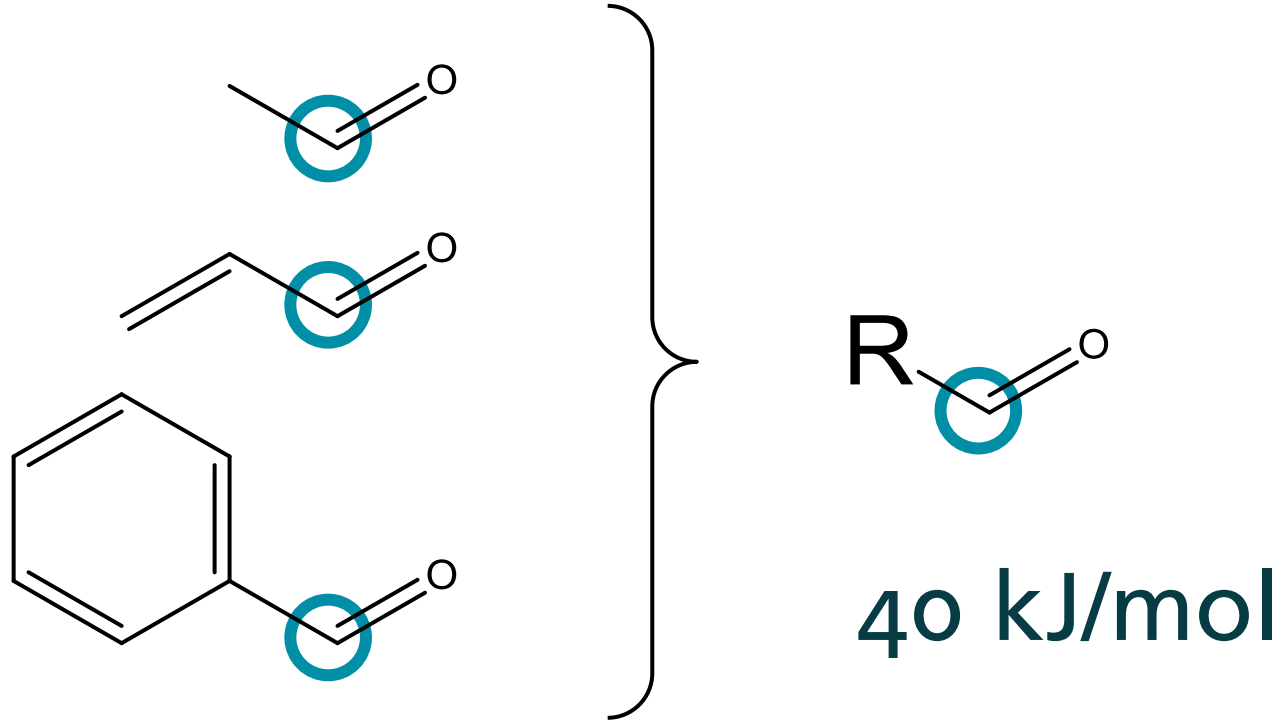

O
H3C


N
N
O
Fe
SCH3
N
N

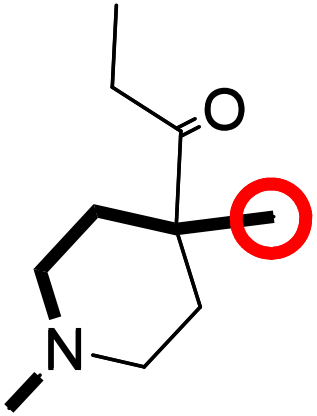
200+ Transition States

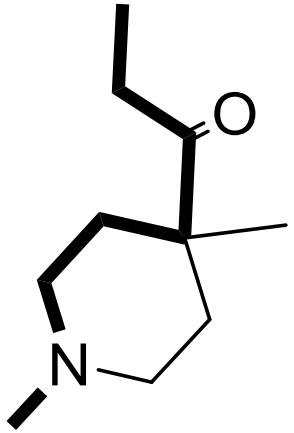
All major reaction types





40 kJ/mol





$Maxbonds_i = 5$

$Maxbonds_{all} = 7$

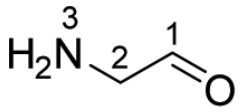
Accessibility = 5/7 = 0.7

SMARTCyp

Score = Energy – 8*Accessibility

SMARTCyp

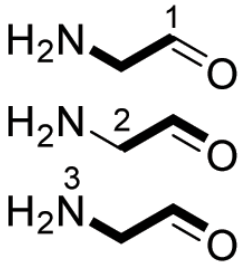
1. Assign Energies By SMARTS matching



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

$A_i = Maxbonds_i / Maxbonds_{all}$



$A_1 = 2 / 3 = 0.67$

$A_2 = 2 / 3 = 0.67$

$A_3 = 3 / 3 = 1.00$

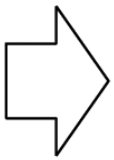
3. Compute Score and Rank Atoms

Score, S = E - 8A
Lowest score gets rank 1

$S_1 = 40.2 - 8*0.67 = 34.84$

$S_2 = 39.8 - 8*0.67 = 34.44$

$S_3 = 54.1 - 8*1.00 = 46.10$

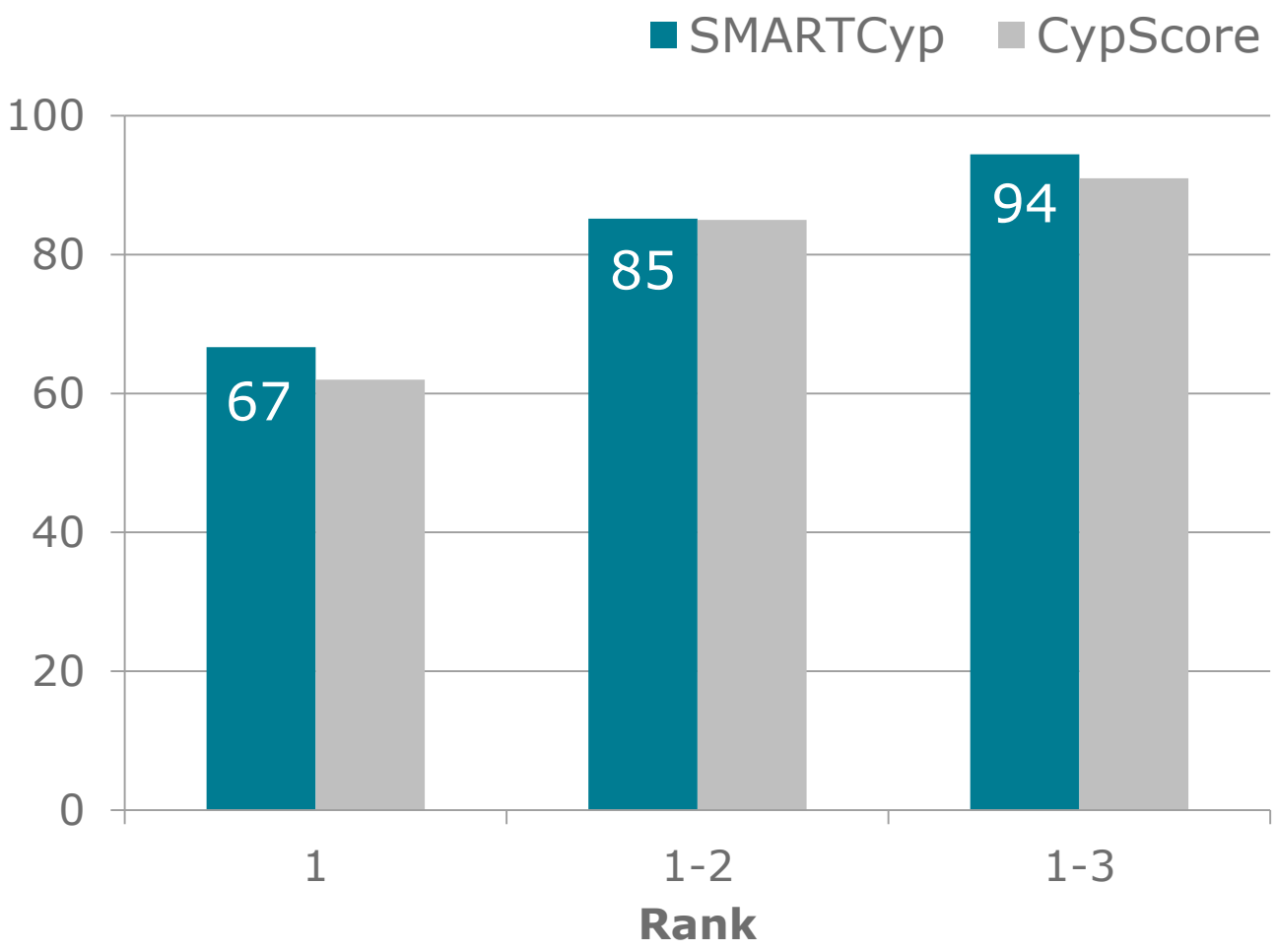


Atom 1 - Rank 2

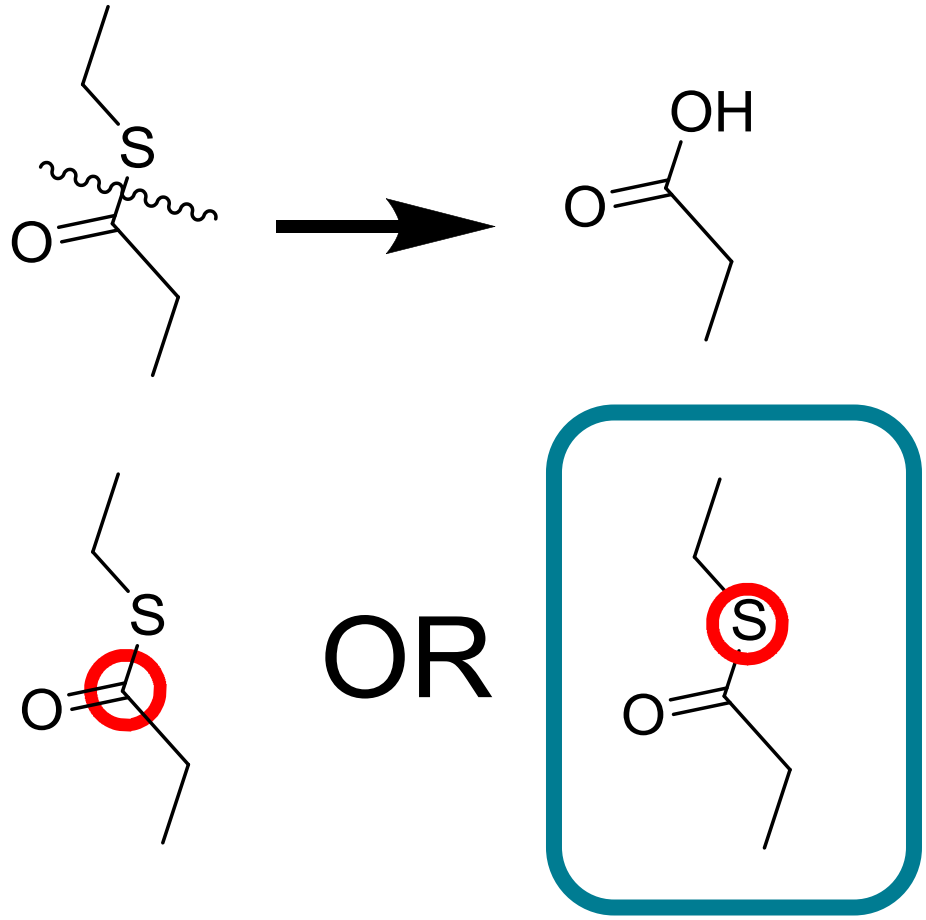
Atom 2 - Rank 1

Atom 3 - Rank 3

Isoform Unspecific Metabolism



Database Problems



False negatives

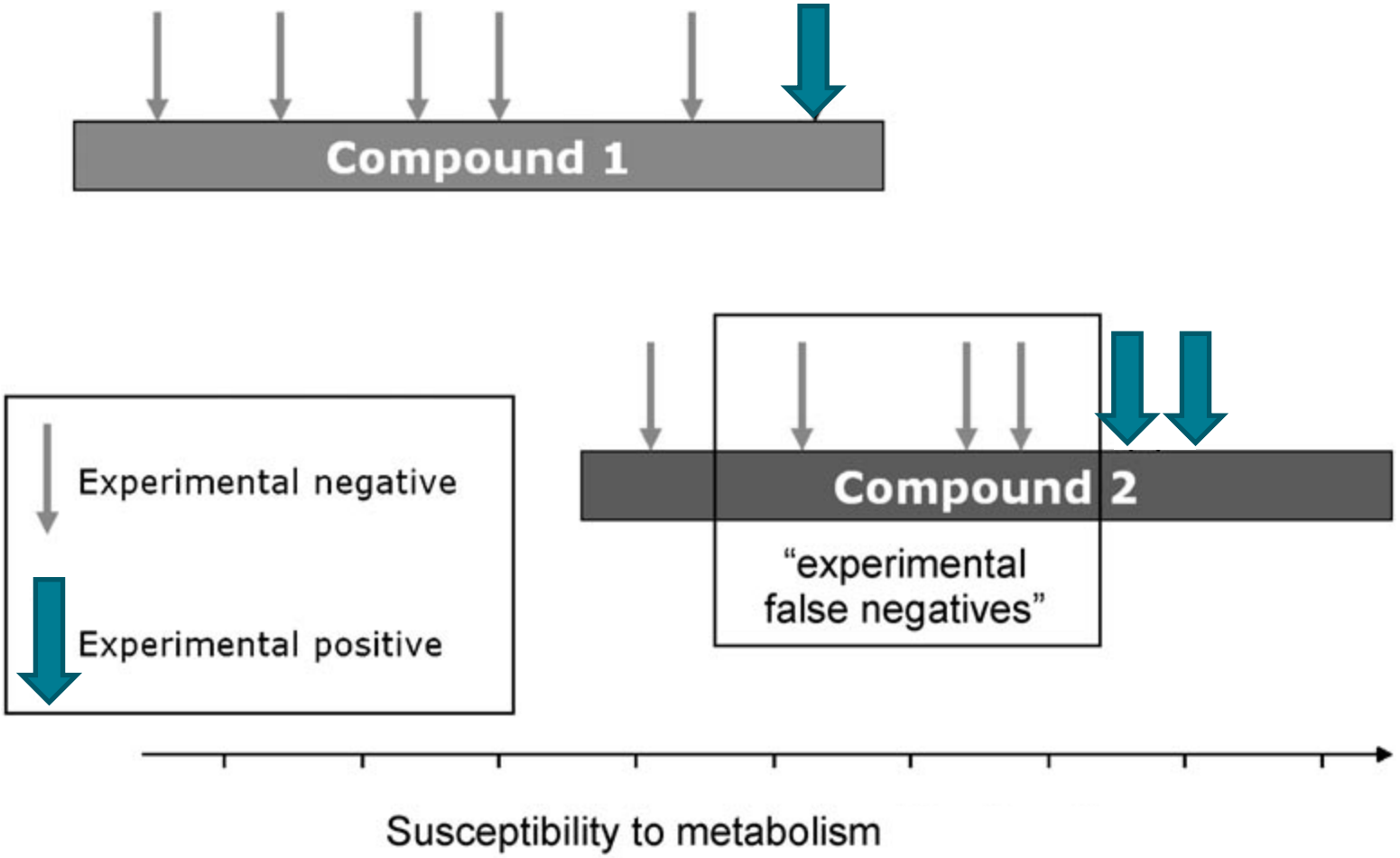
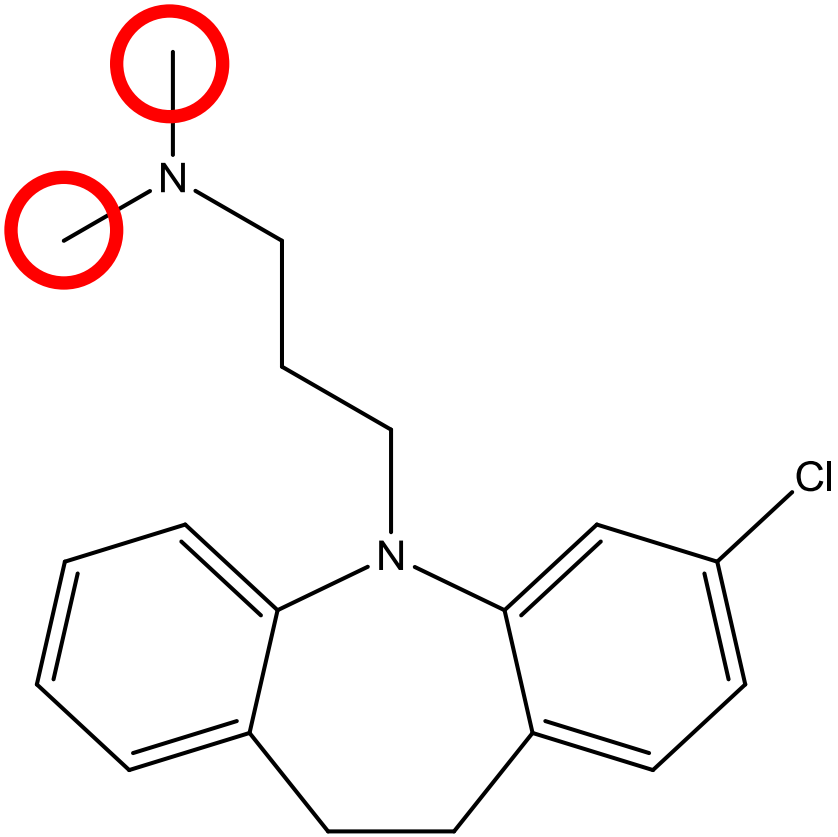
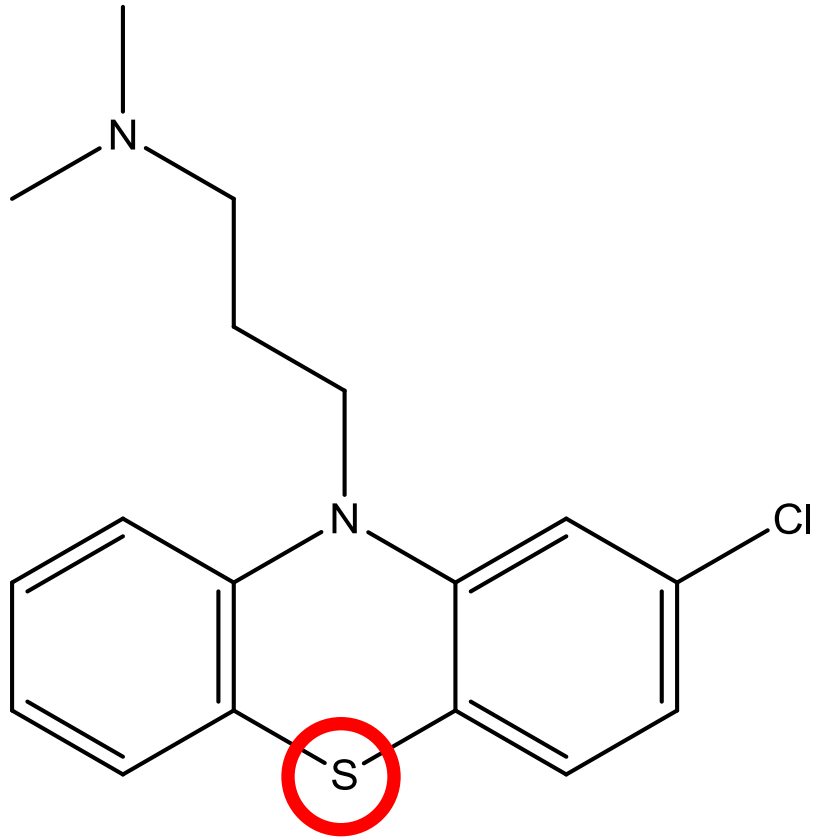


Image from: M. Hennemann et al., ChemMedChem, 2009, 4, 657-669

False negatives – N-dealkylation

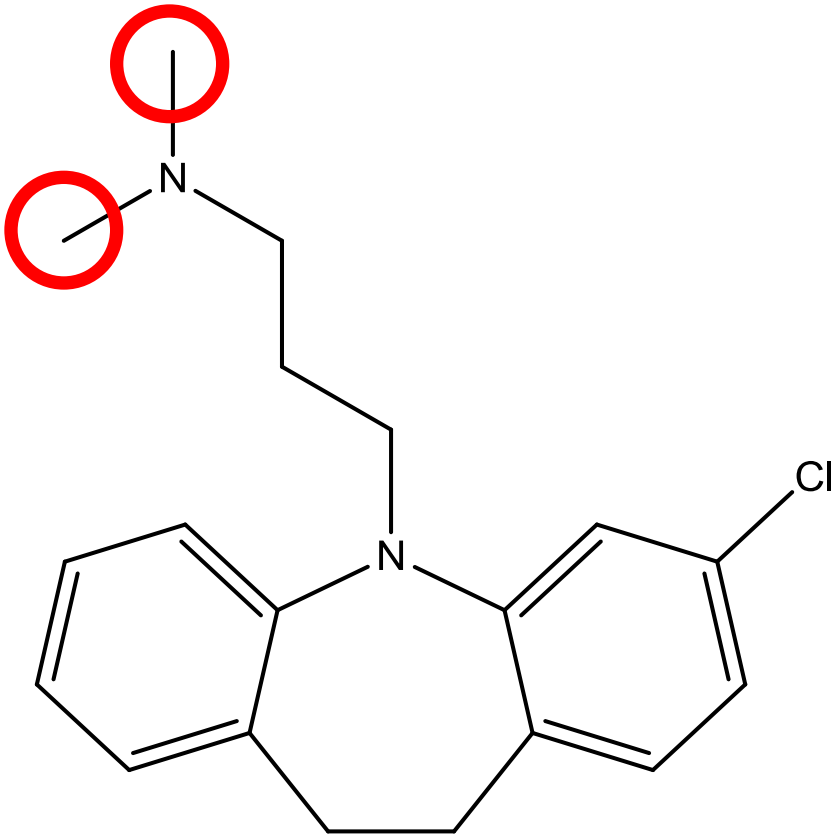


Clomipramine

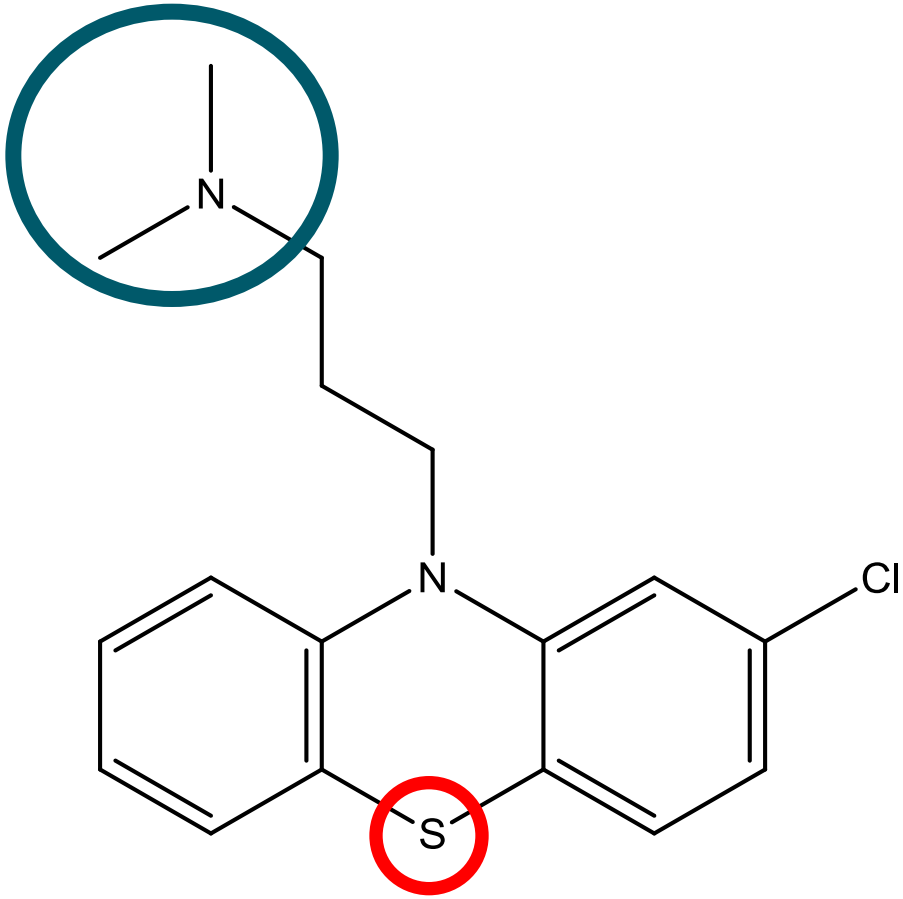


Chlorpromazine

False negatives – N-dealkylation

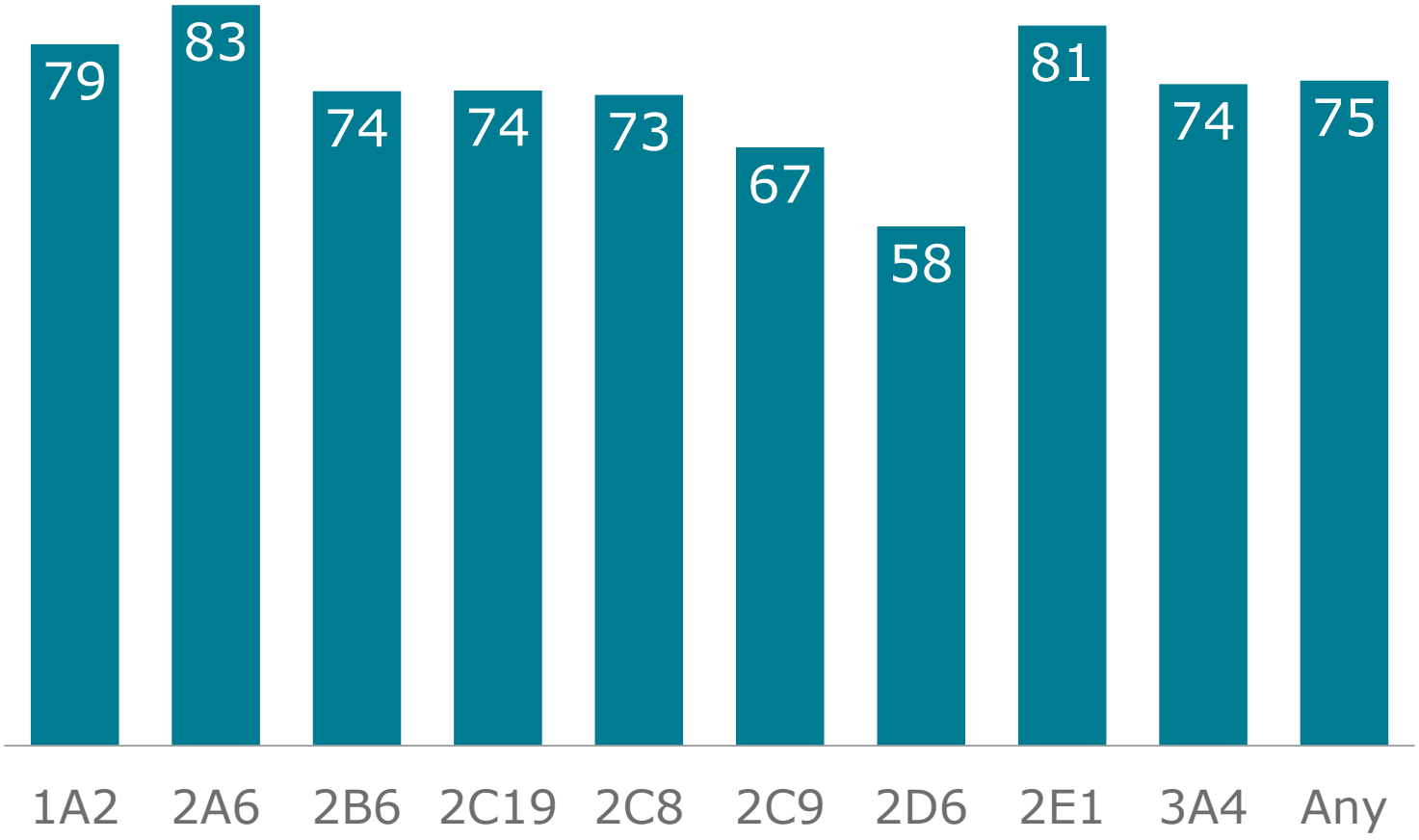


Clomipramine

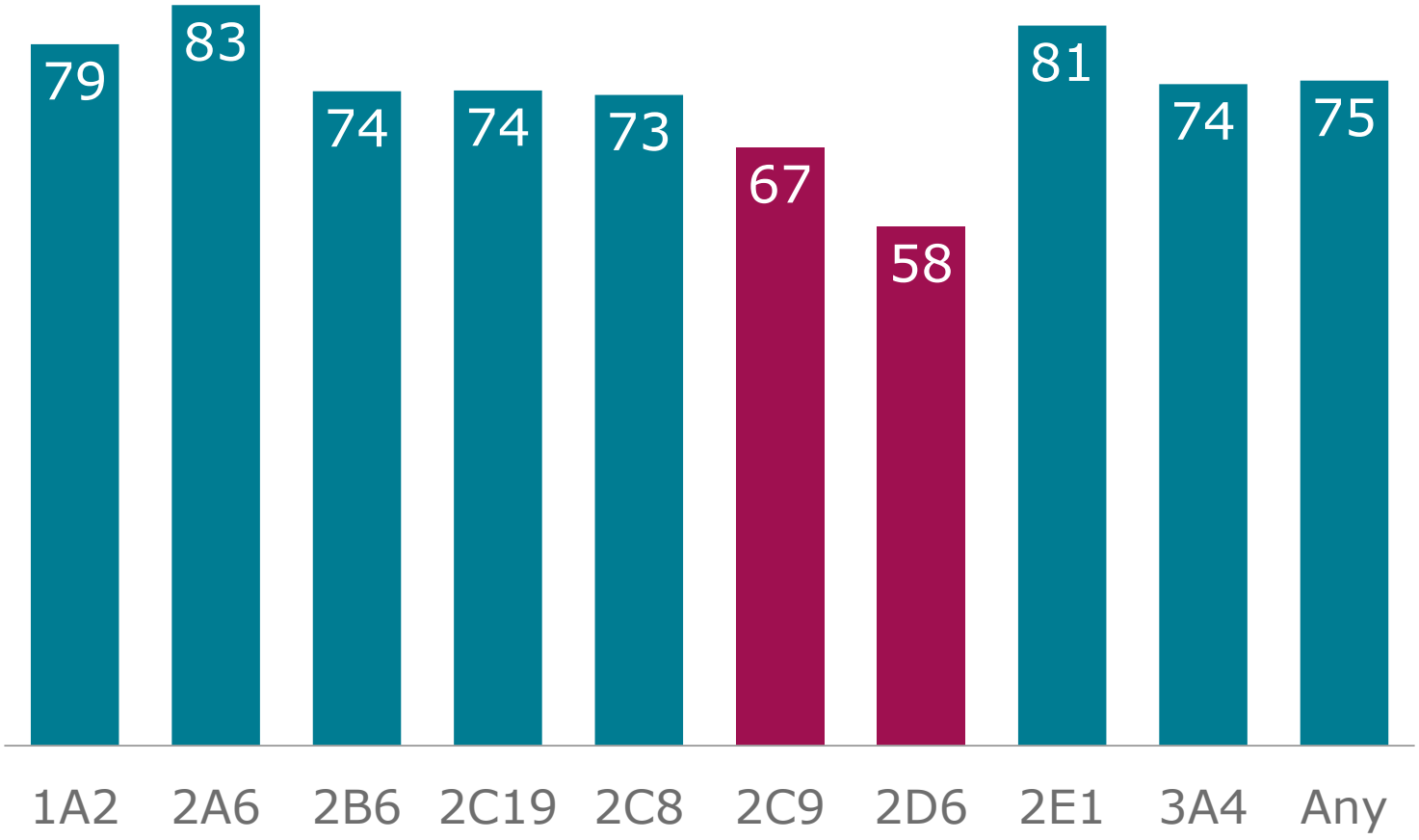


Chlorpromazine

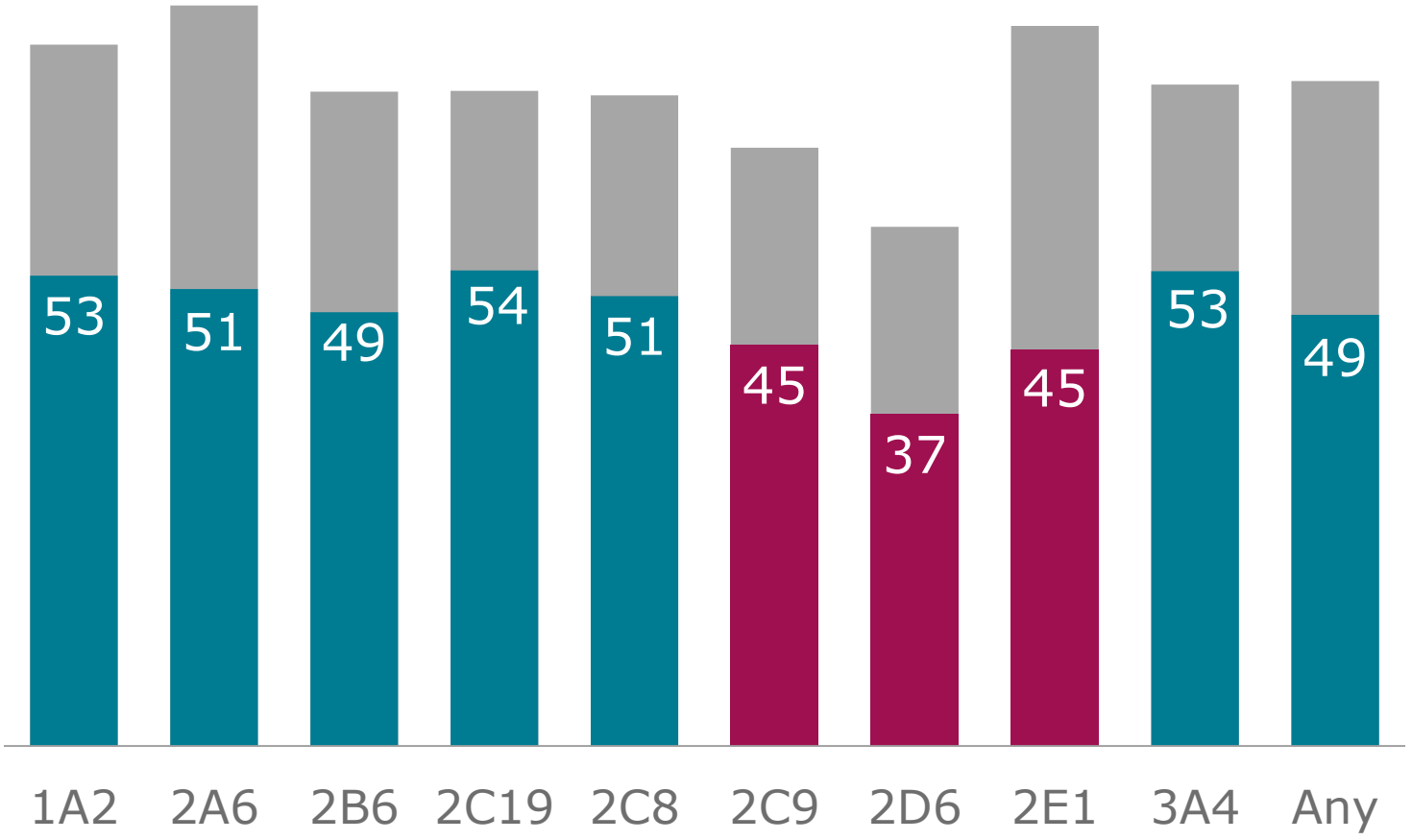
SMARTCyp Accuracy for Nine Isoforms



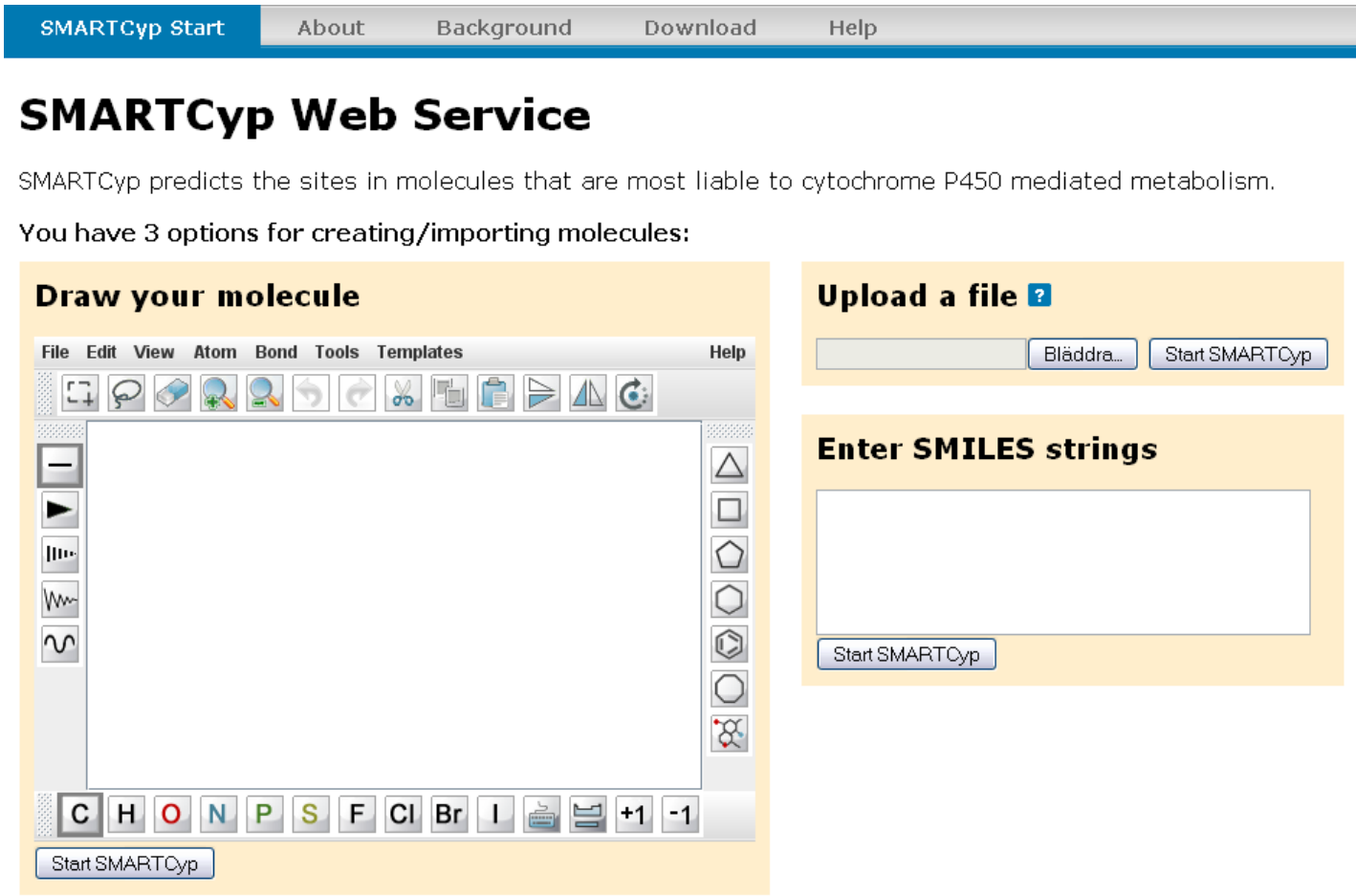
SMARTCyp Accuracy for Nine Isoforms



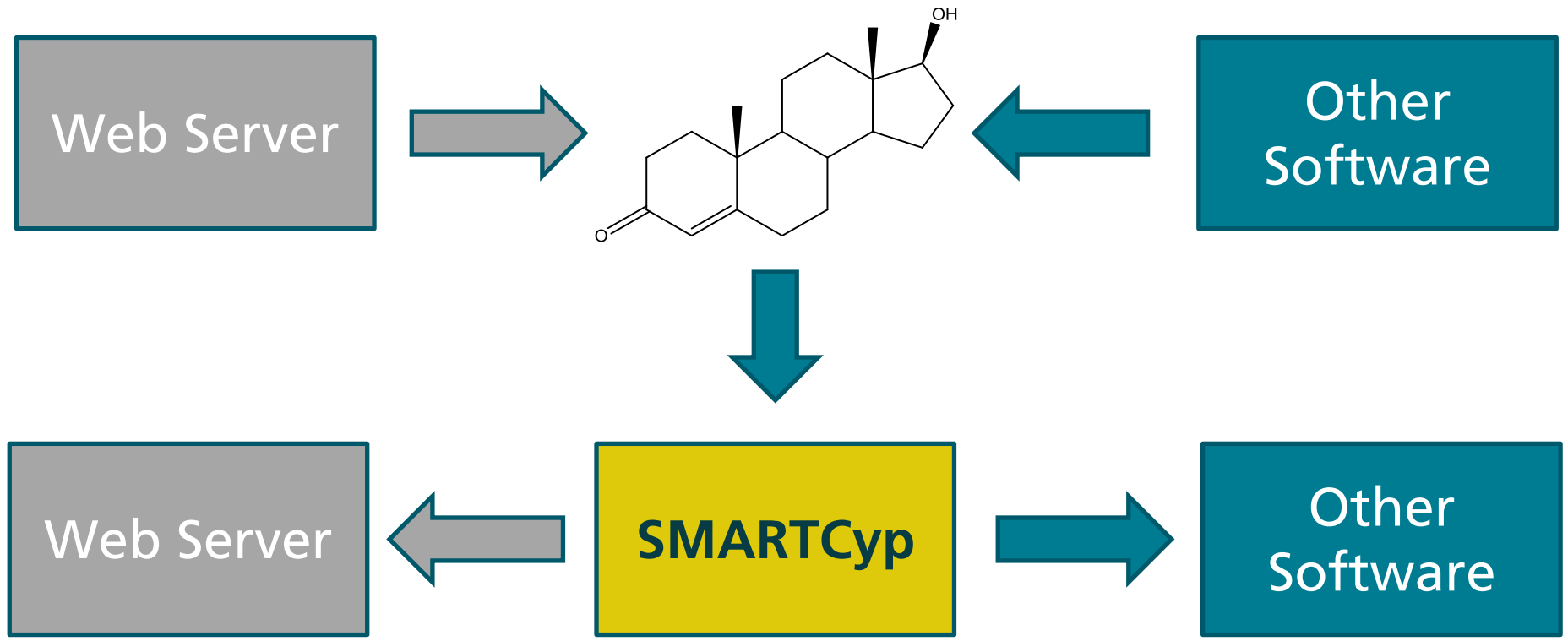
Enrichment


53
51
49
54
51
45
37
45
53
49
1A2
2A6
2B6
2C19
2C8
2C9
2D6
2E1
3A4
Any

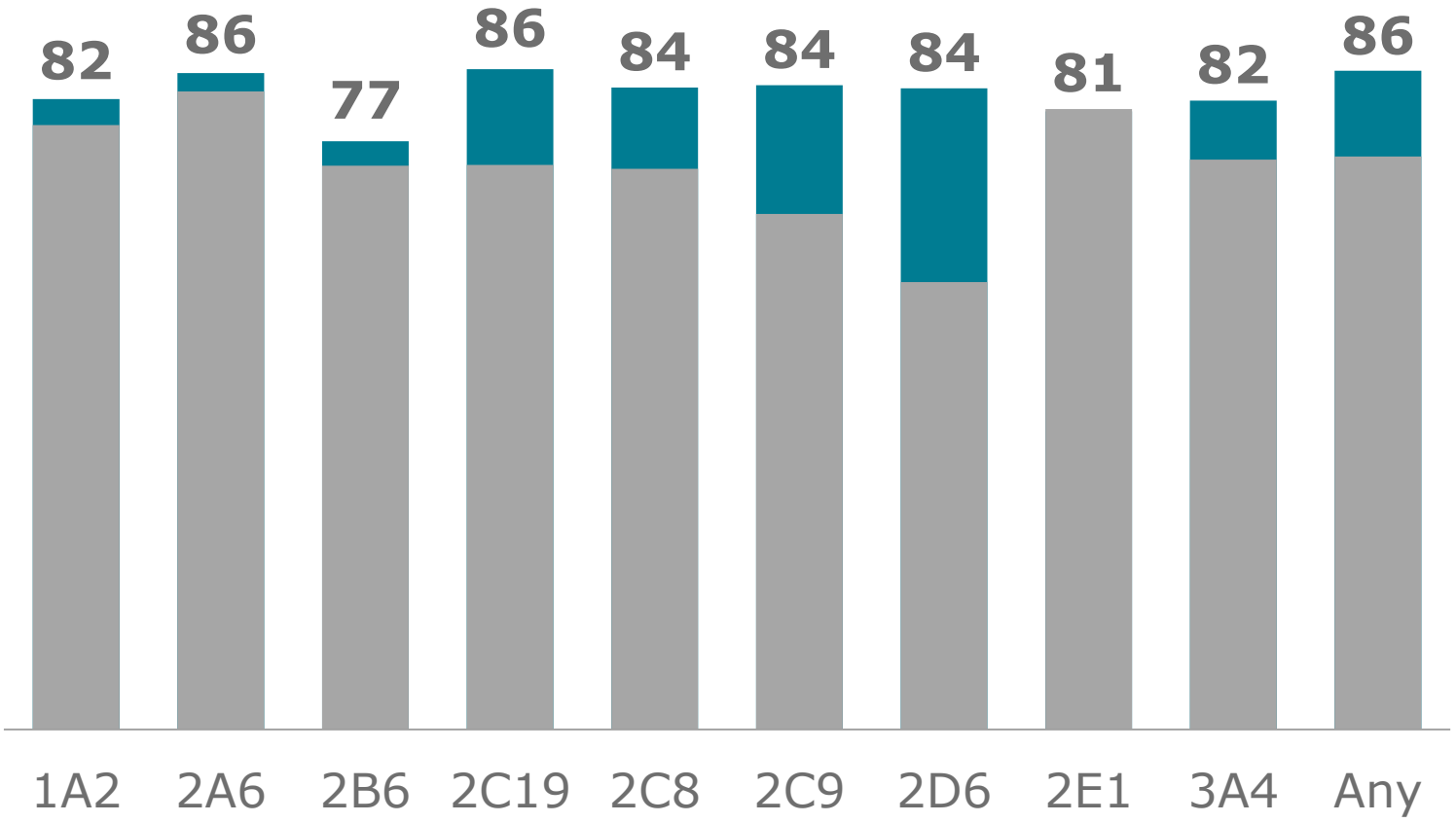
www.farma.ku.dk/smartcyp/



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”

Acknowledgements

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