



optibrium

Challenges and Recent Developments in the Prediction of Cytochrome P450 Mediated Site of Metabolism

Patrik Rydberg, PhD

Associate Director, Computational Chemistry

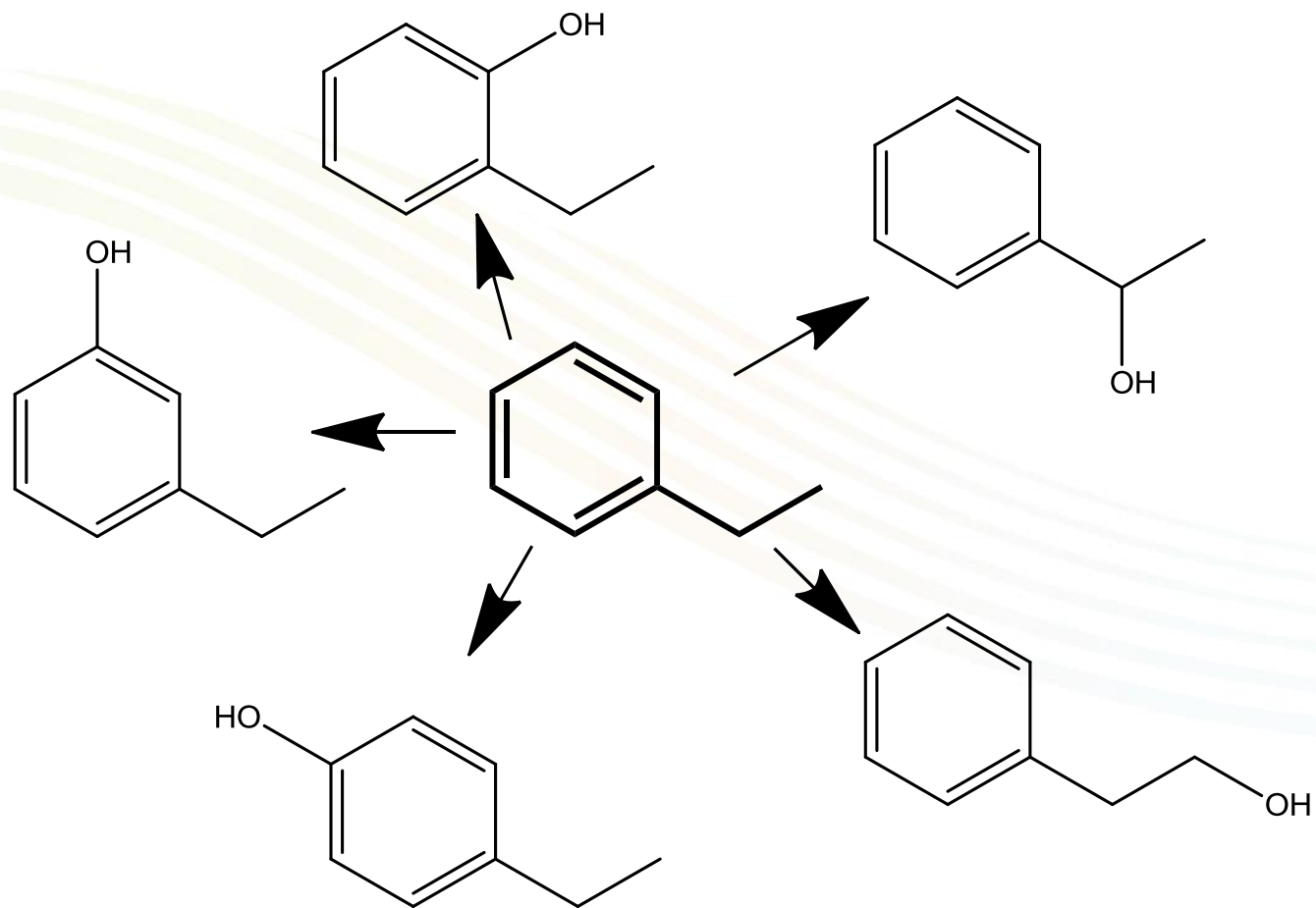
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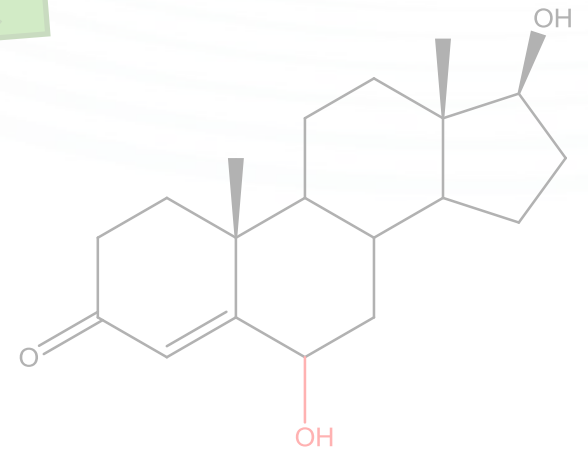
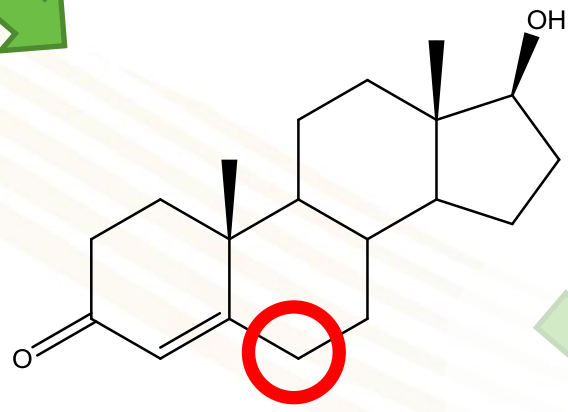
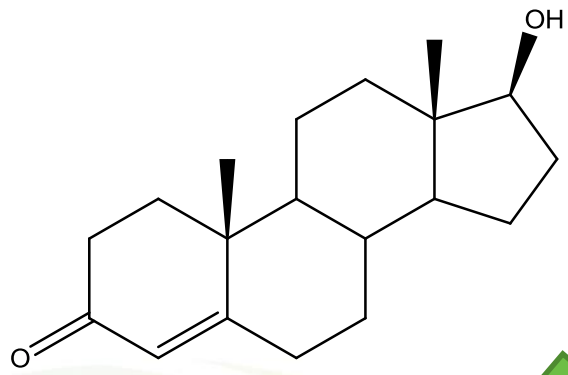
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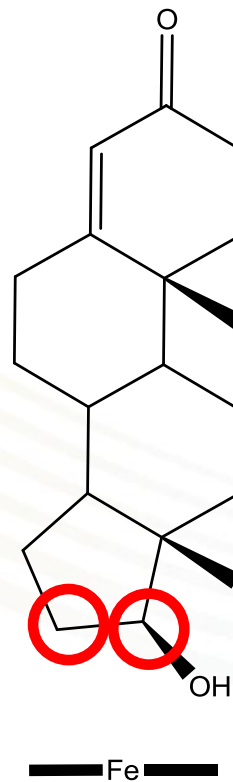
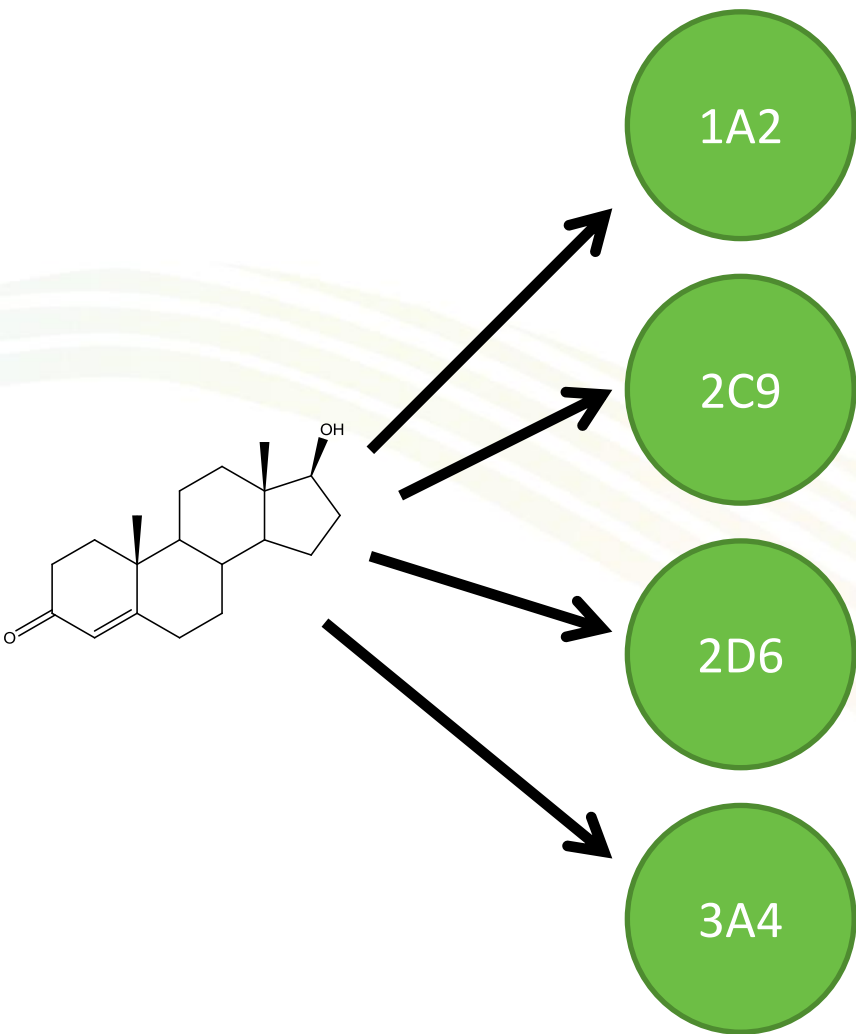
Site of Metabolism Prediction



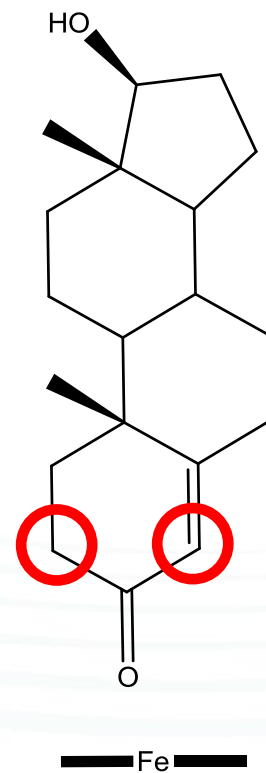


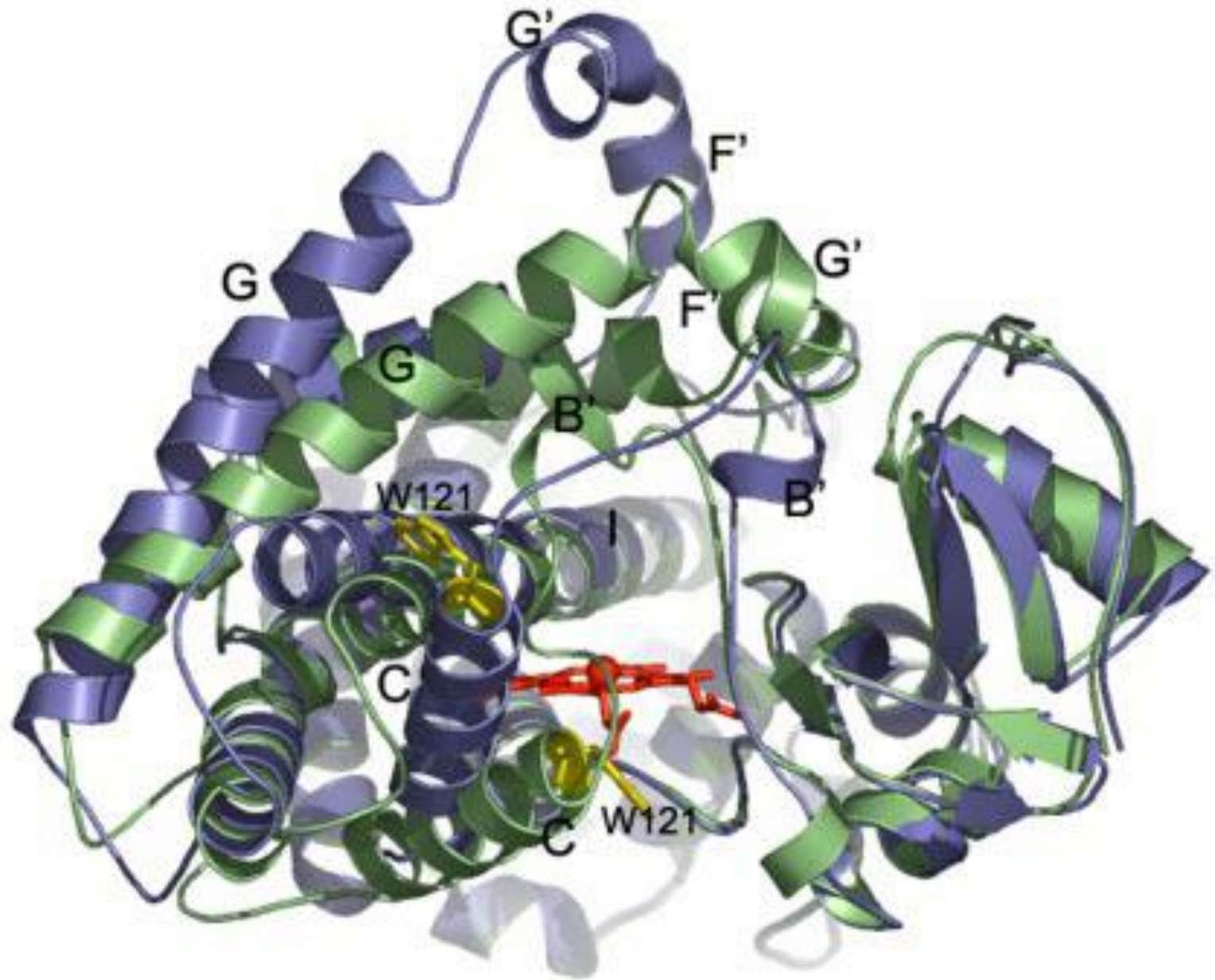
Why is it hard?

The slide features a large, bold title 'Why is it hard?' in a dark red font at the top left. Below the title, several wavy, overlapping lines in shades of light green and blue sweep across the middle of the slide, creating a sense of movement and depth.



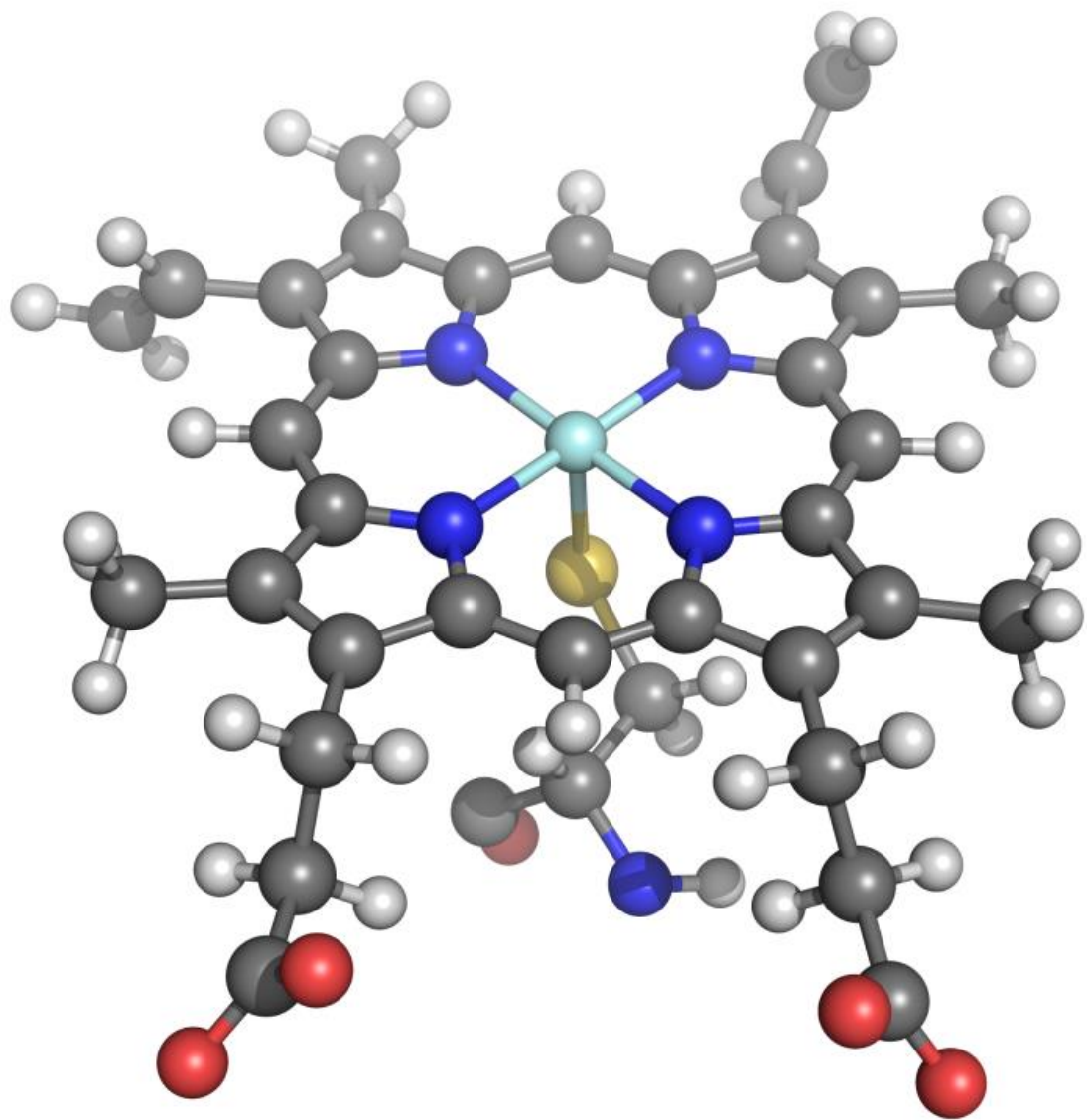
OR/AND

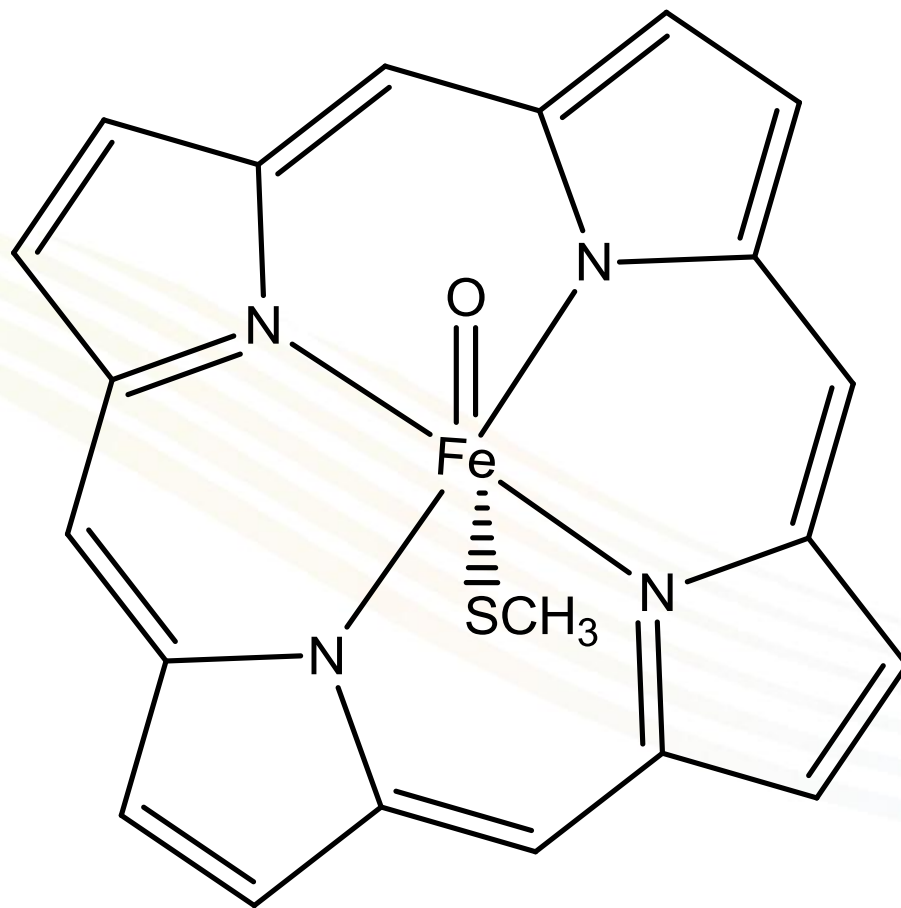


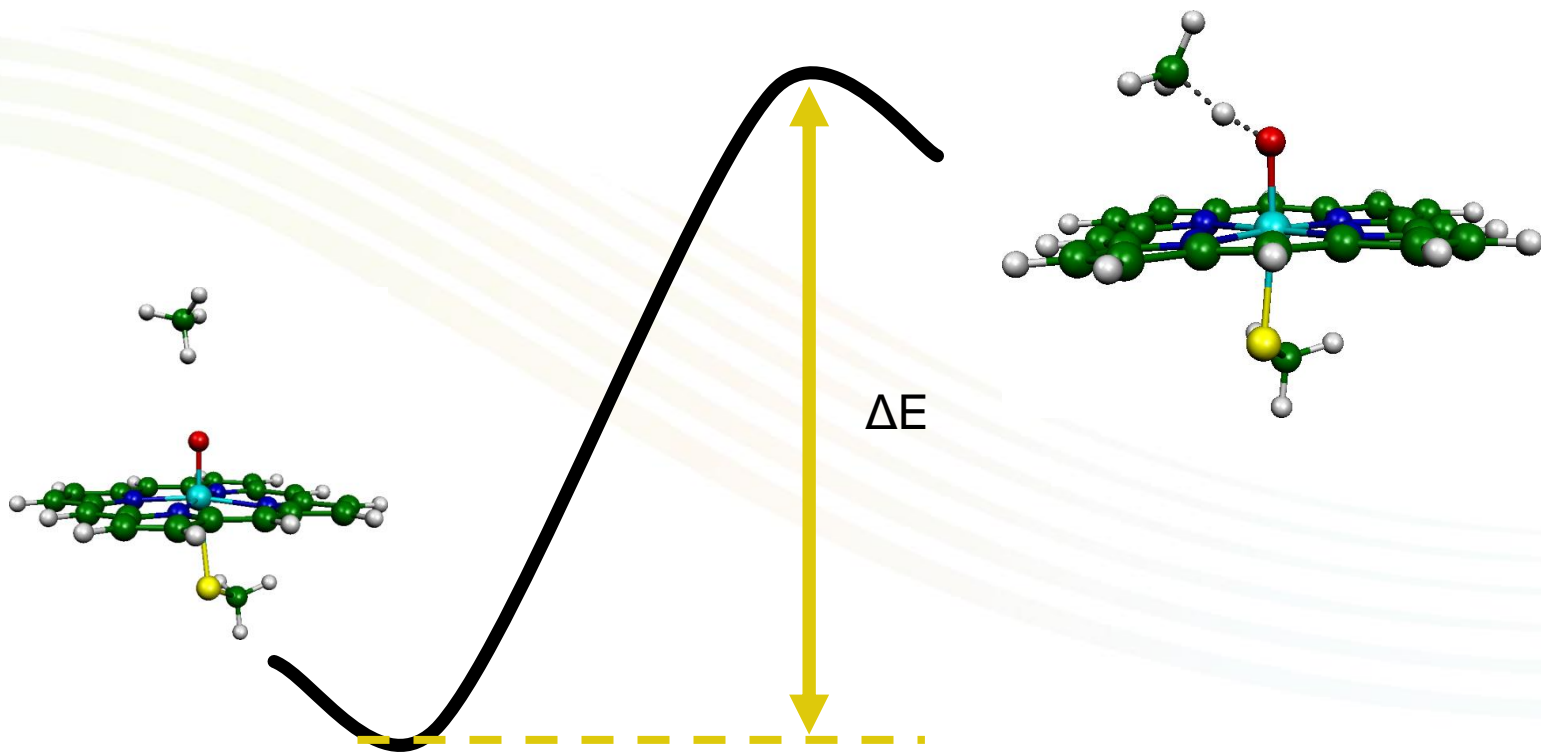




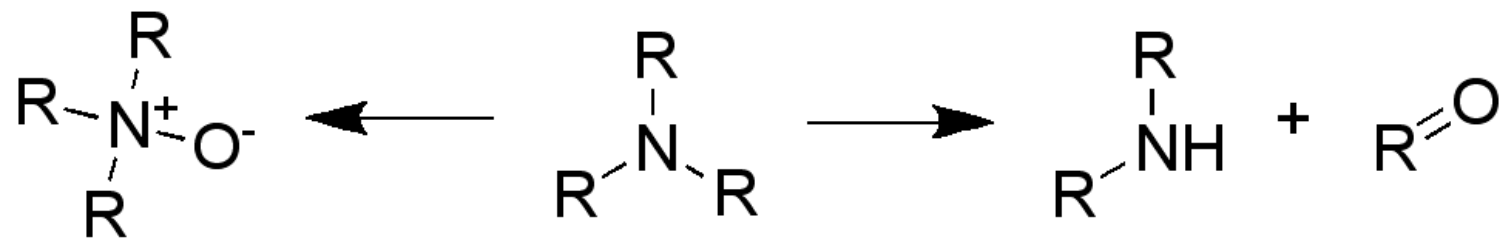
Free rotation!



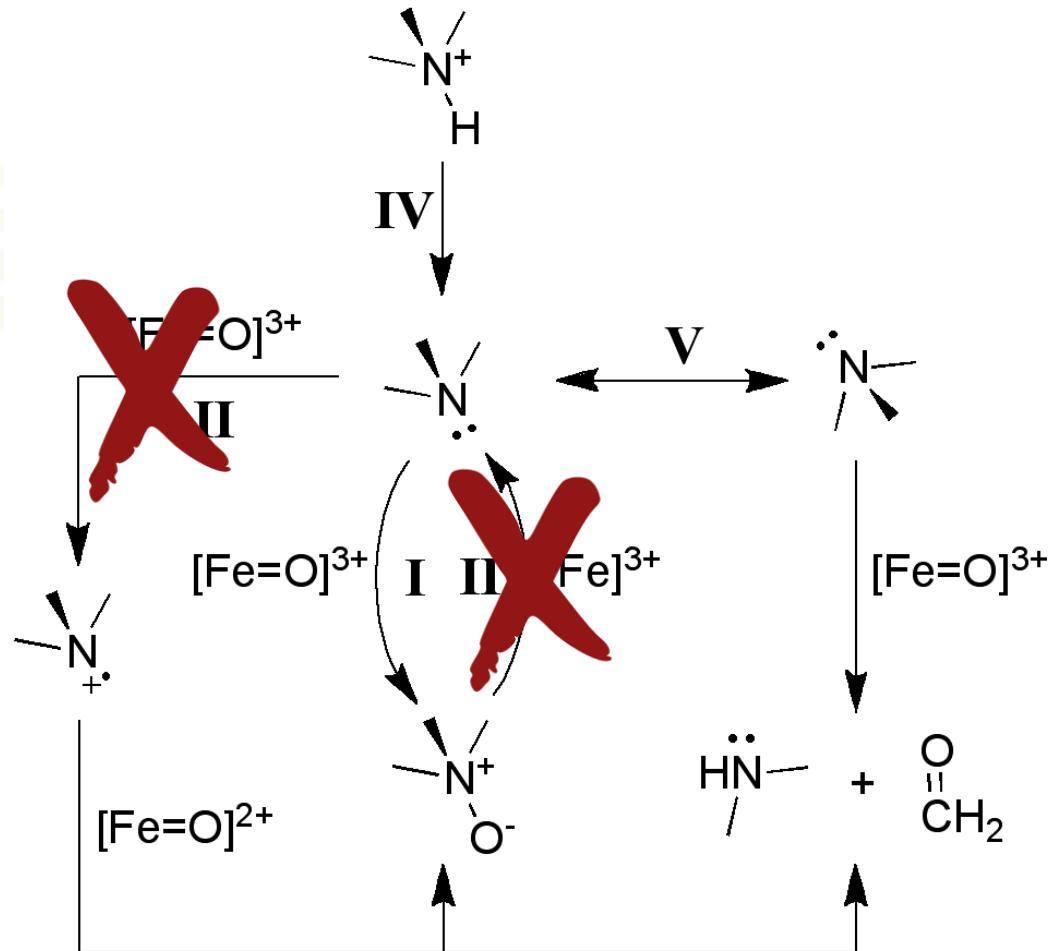




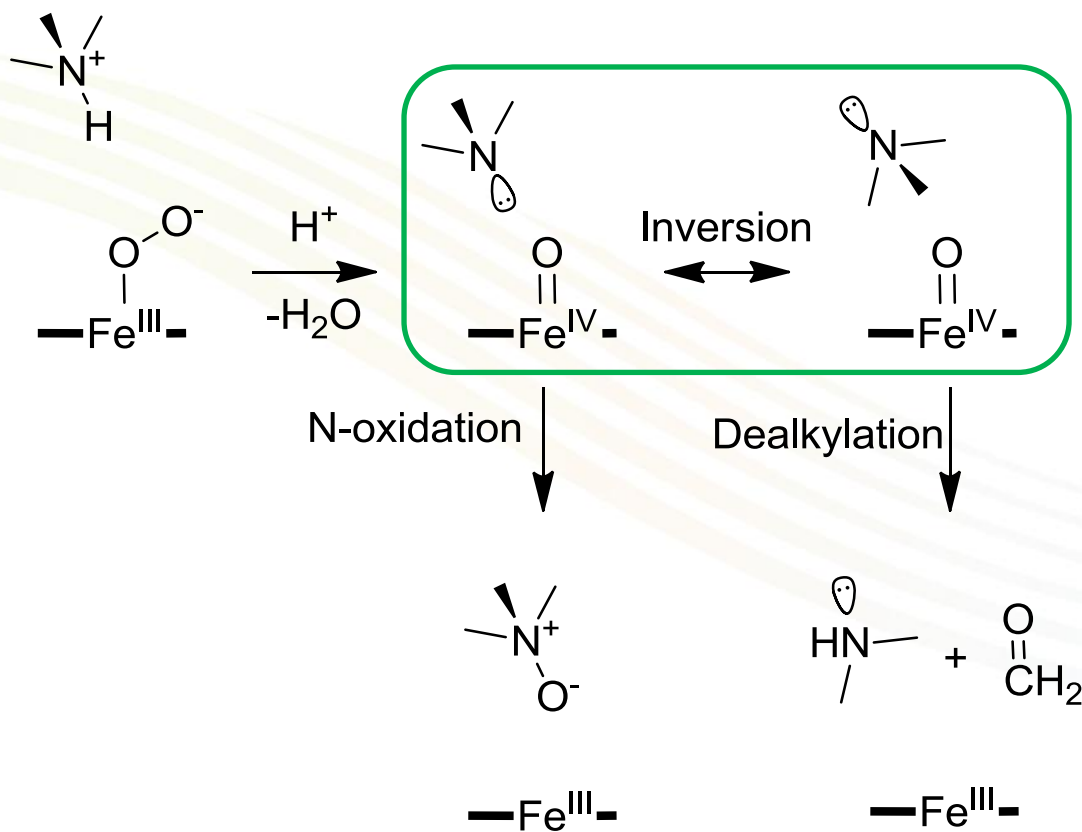
N-oxidations – Tertiary Amines



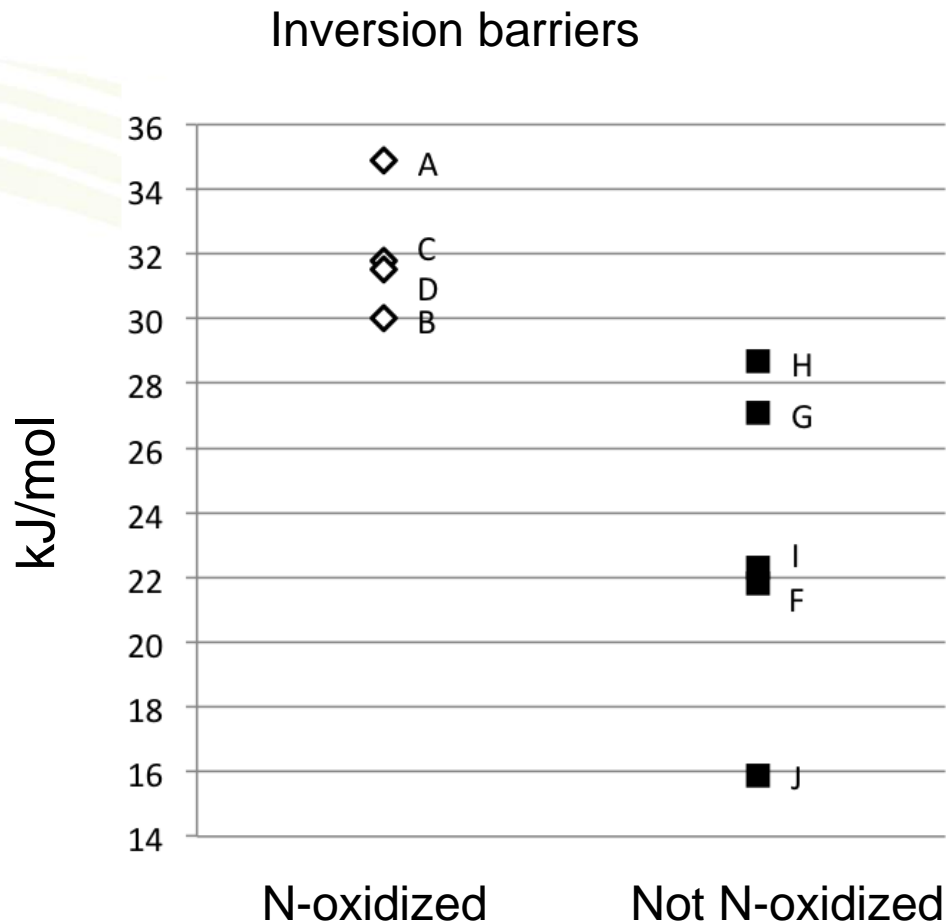
N-oxidations – Tertiary Amines



N-oxidations – Tertiary Amines



N-oxidations – Tertiary Amines



Rydborg et al., *Angewandte Chemie*, 2013, 52, 993-997

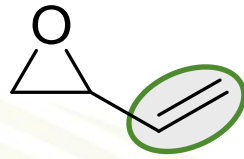
Epoxidation vs. Hydroxylation



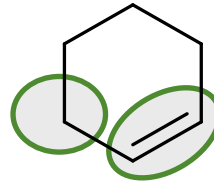
Major



Minor



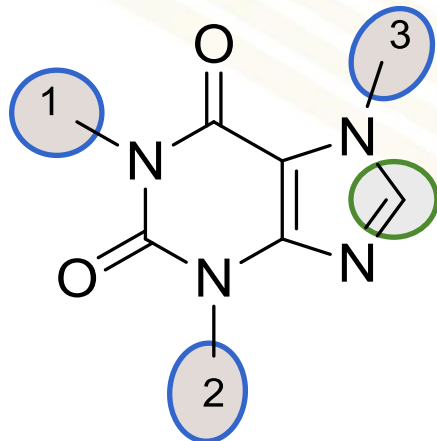
butadiene
monoxide



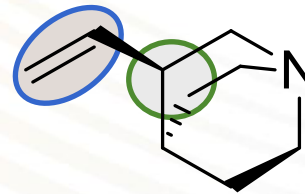
cyclohexene



propene



caffeine



quinidine
fragment

B3LYP



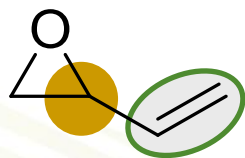
Major



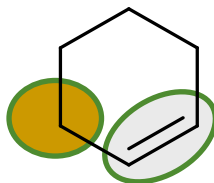
Minor



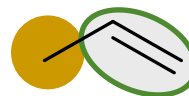
Predicted



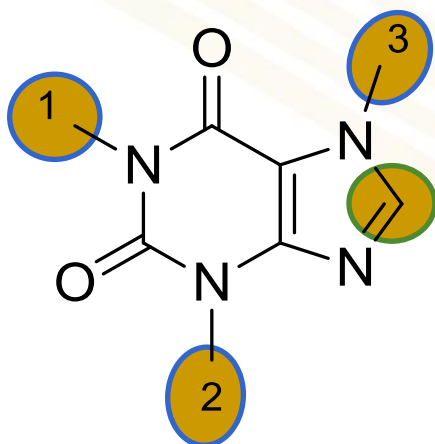
butadiene
monoxide



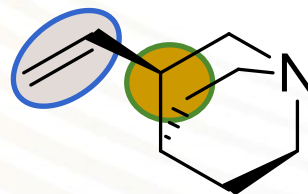
cyclohexene



propene



caffeine



quinidine
fragment

B3LYP-D3



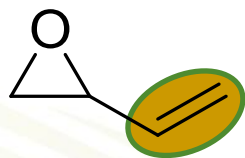
Major



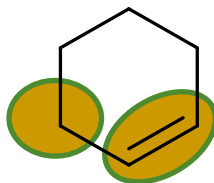
Minor



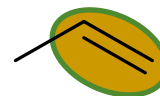
Predicted



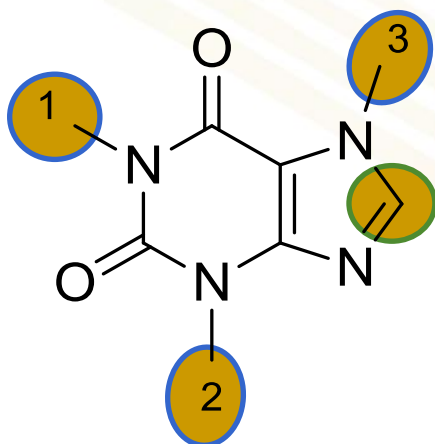
butadiene
monoxide



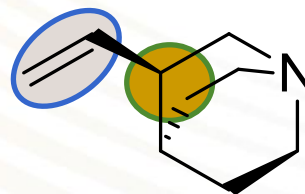
cyclohexene



propene



caffeine

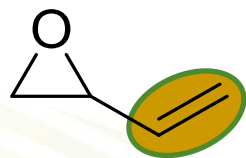


quinidine
fragment

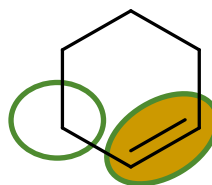
B3LYP without ZPE



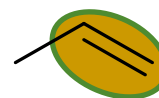
Major



butadiene
monoxide



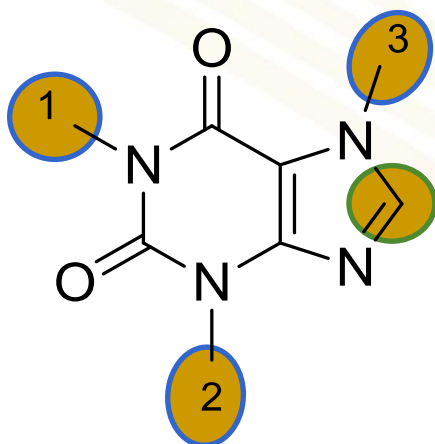
cyclohexene



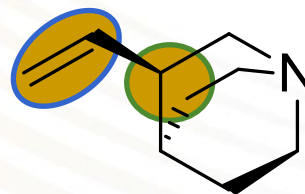
propene



Minor



caffeine



quinidine
fragment



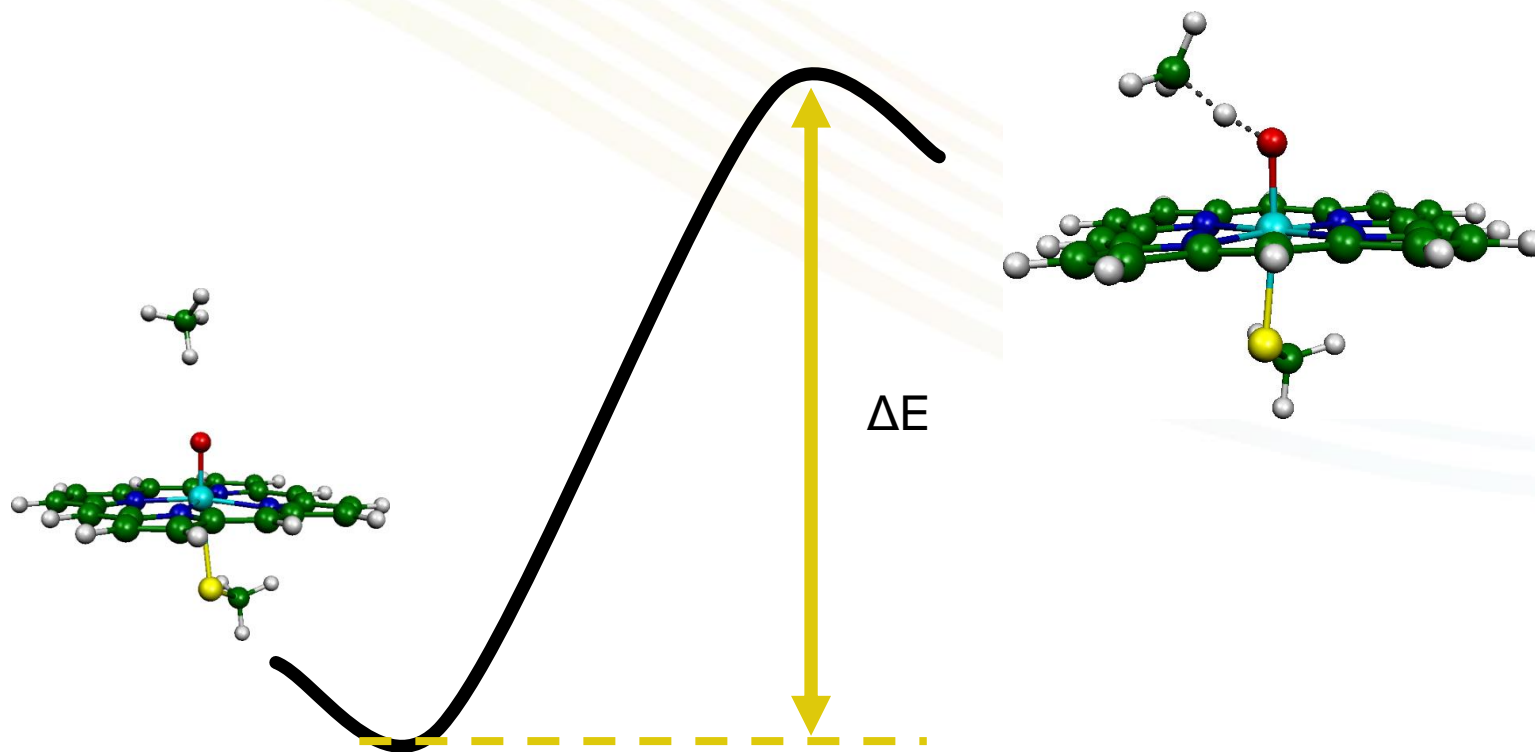
Predicted



SOM Prediction & SMARTCyp

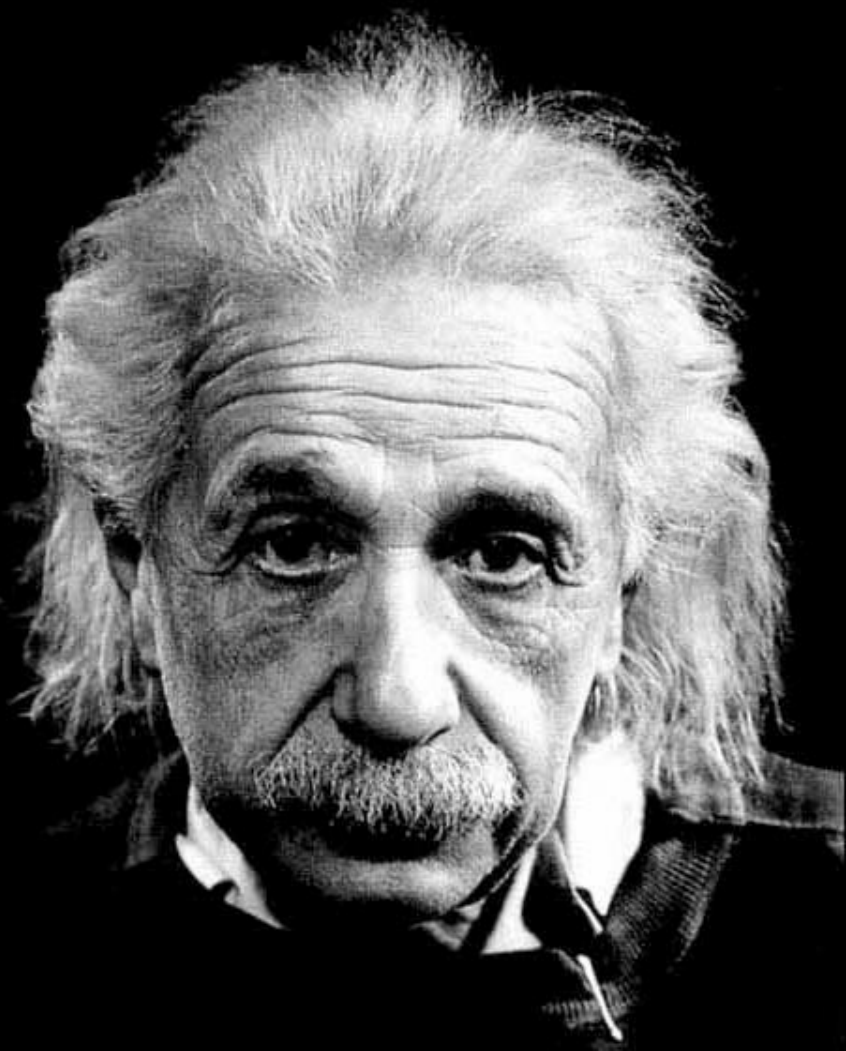
300+ Transition States

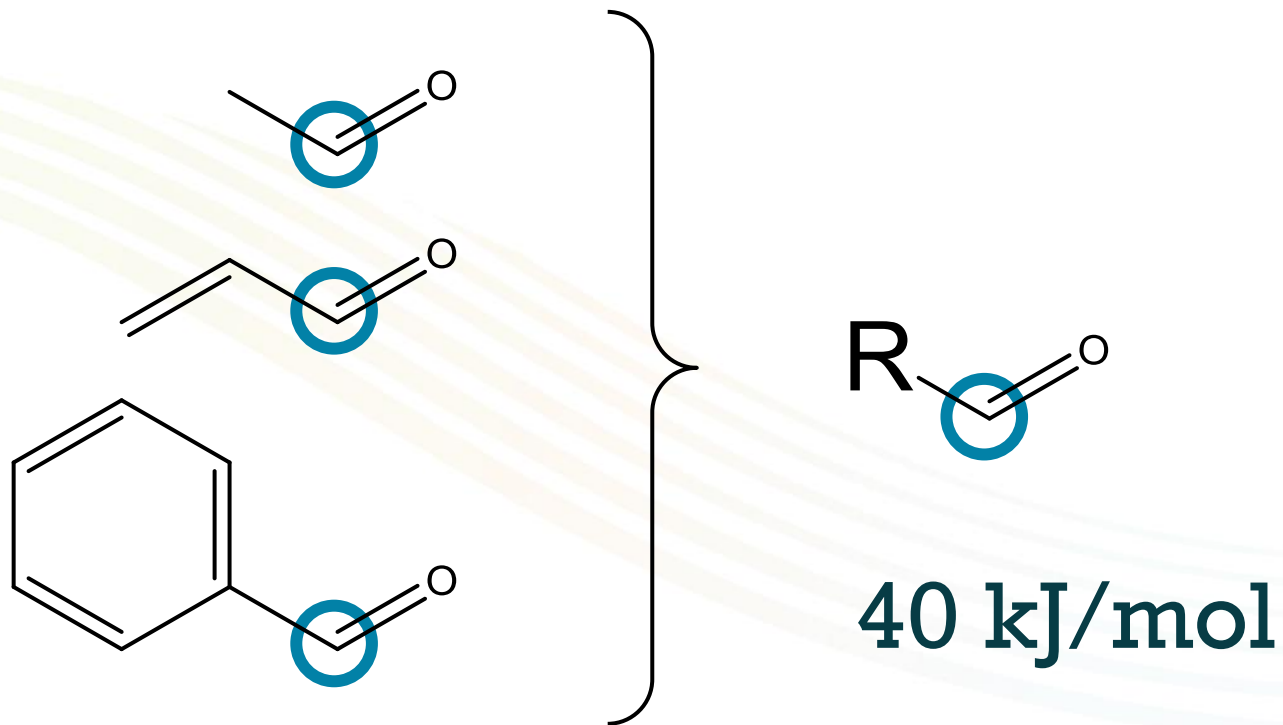
All major reaction types



“Everything should be made
as simple as possible,
but not simpler.”

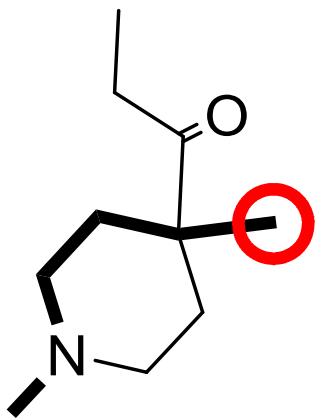
Albert Einstein



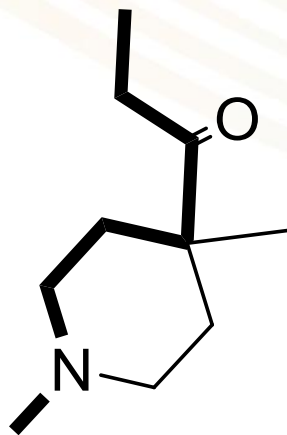


Accessibility

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



$$\text{Maxbonds}_i = 5$$



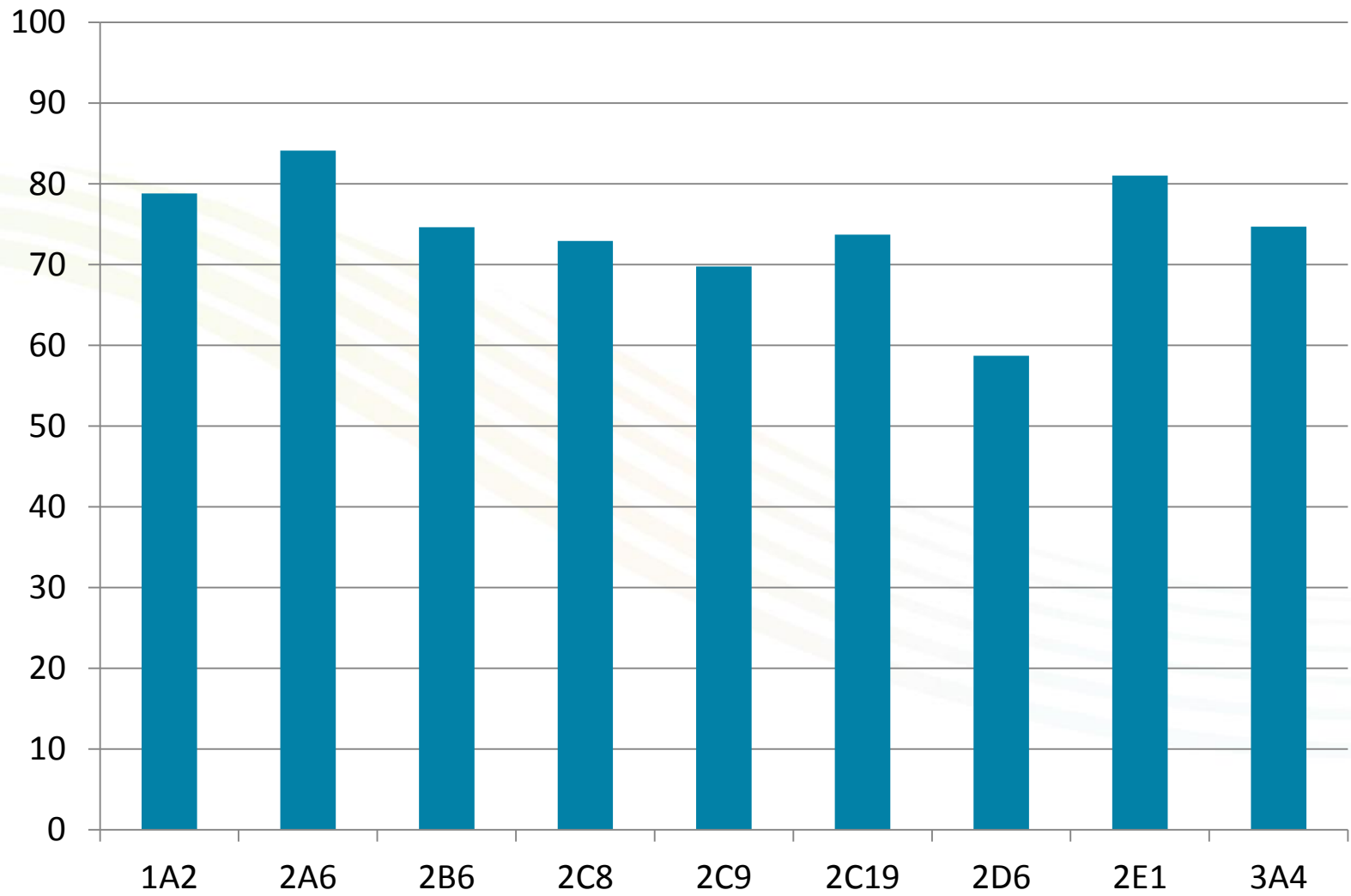
$$\text{Maxbonds}_{\text{all}} = 7$$

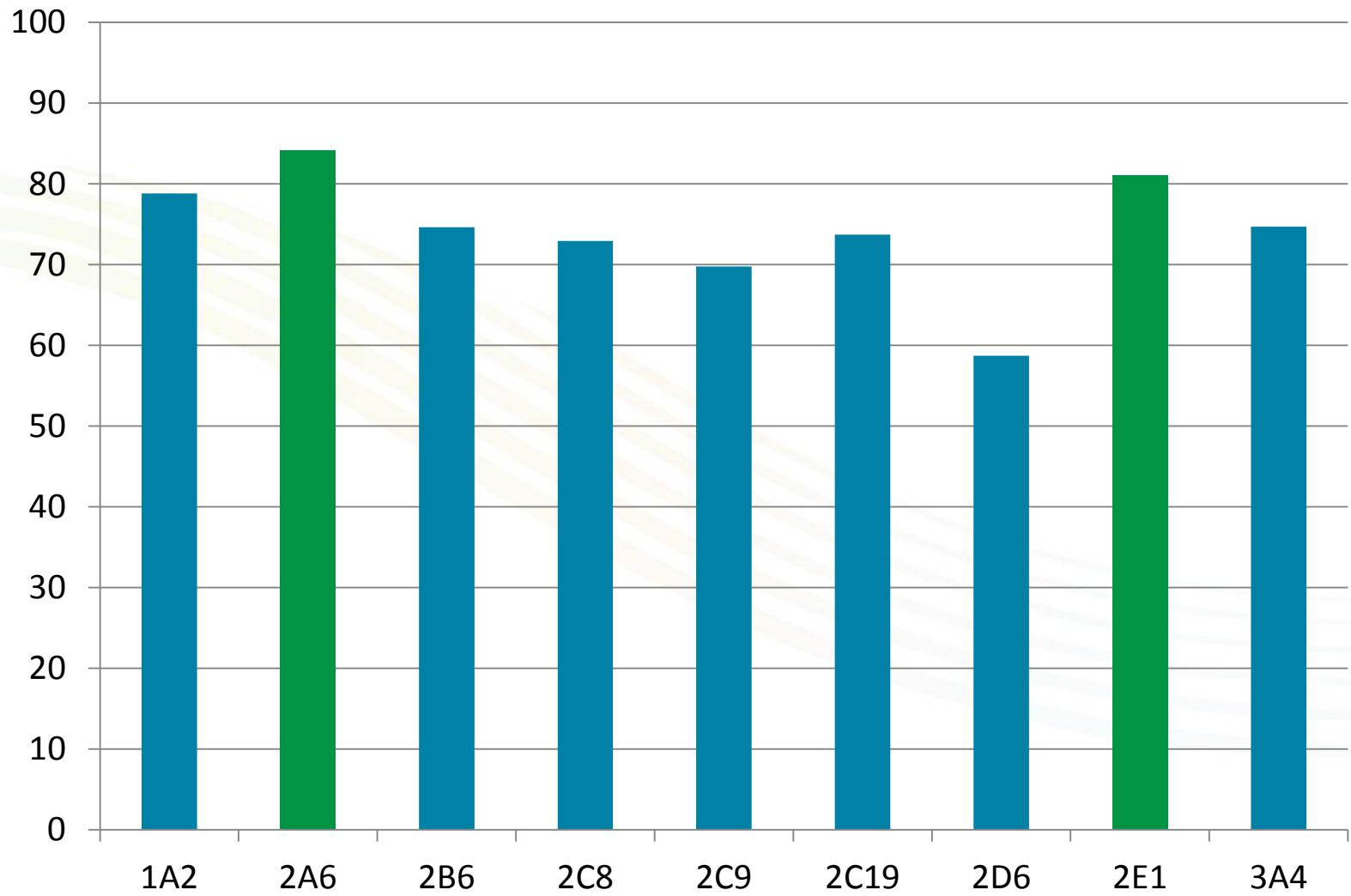
$$A = 5/7 = 0.7$$

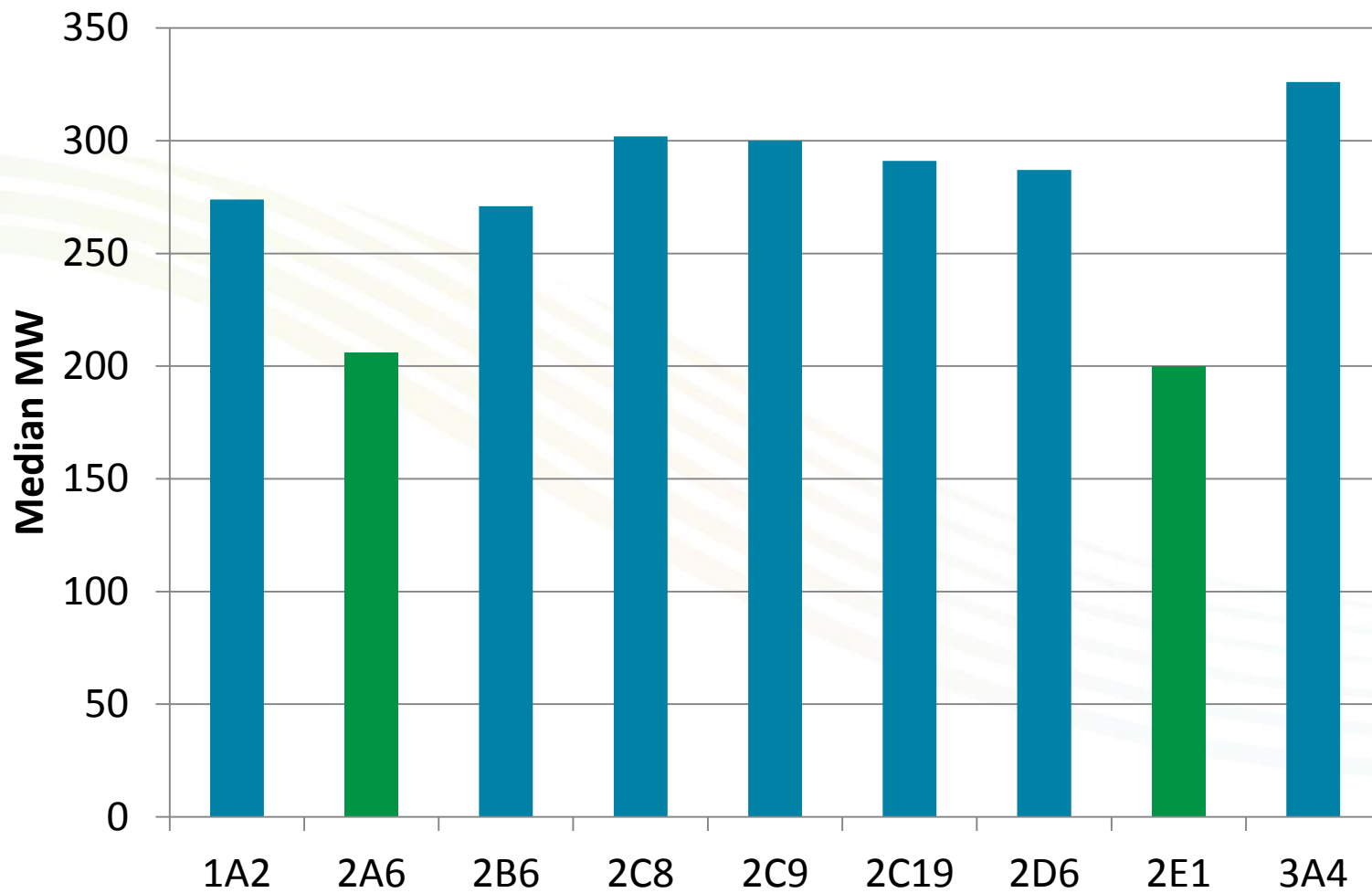


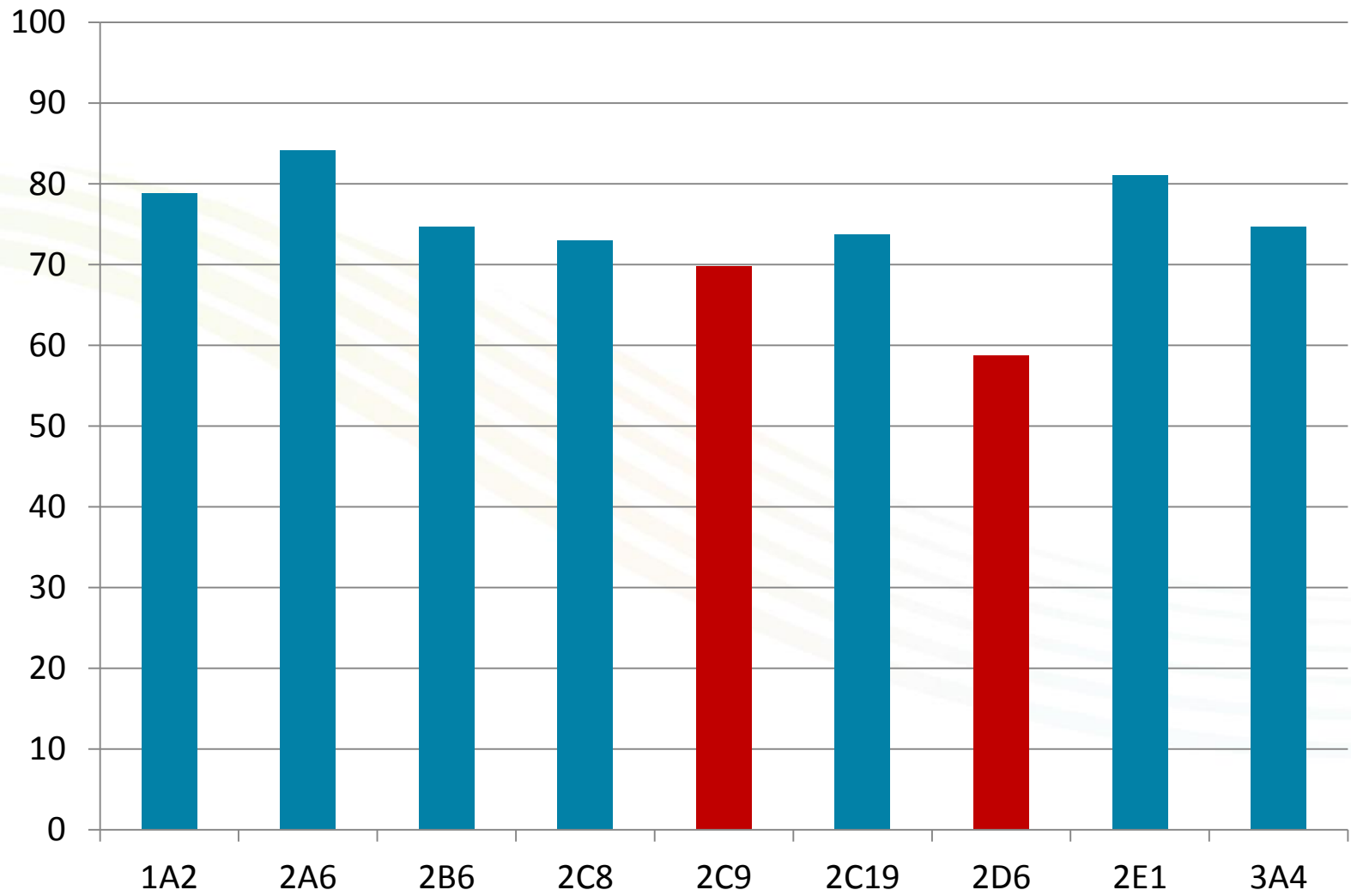
Score = Reactivity – 8*Accessibility

90%

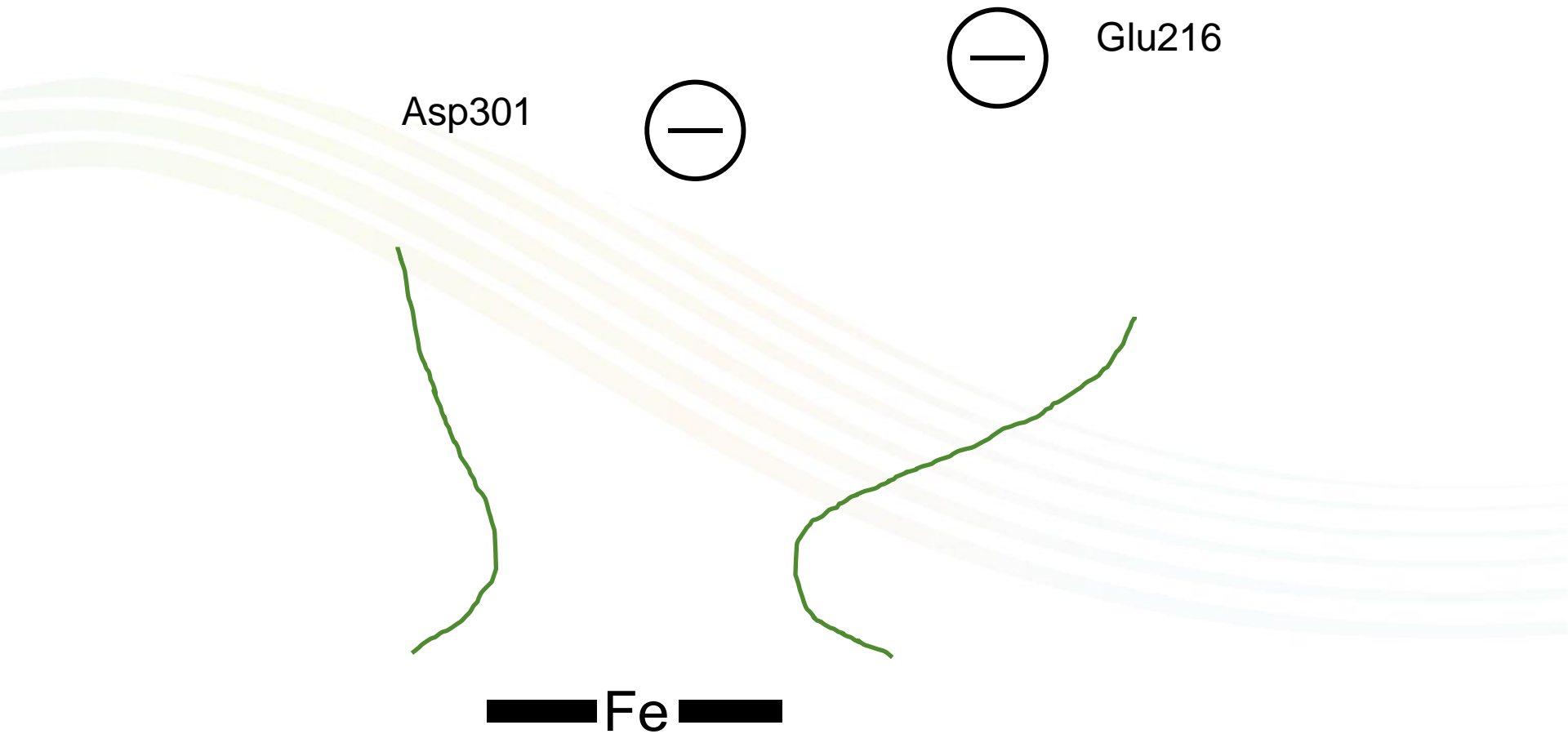




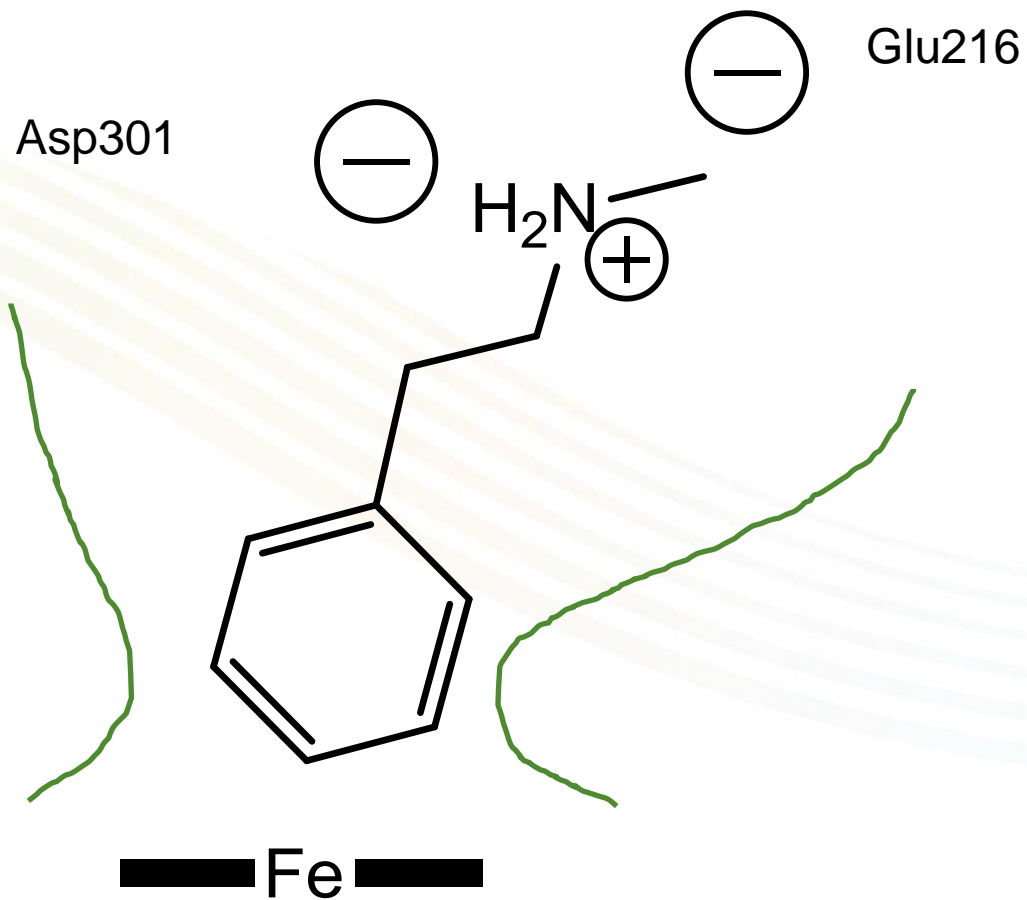




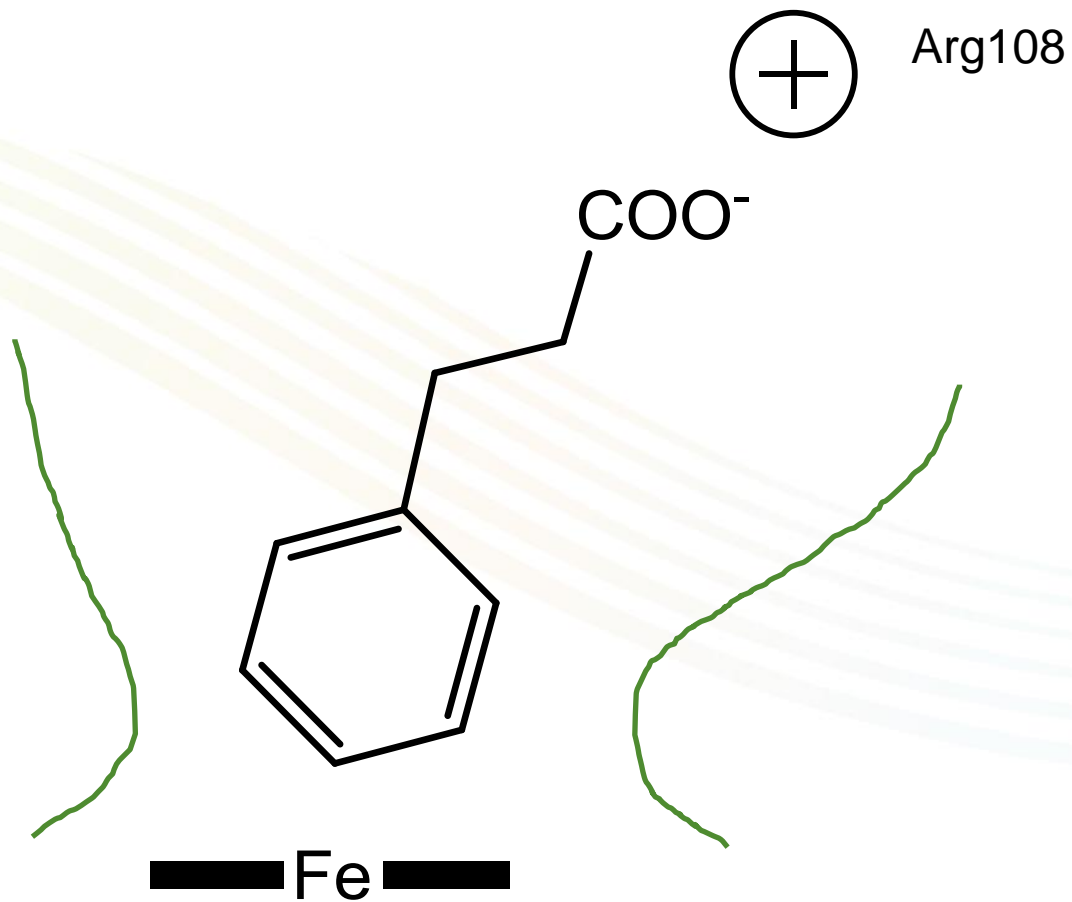
CYP 2D6



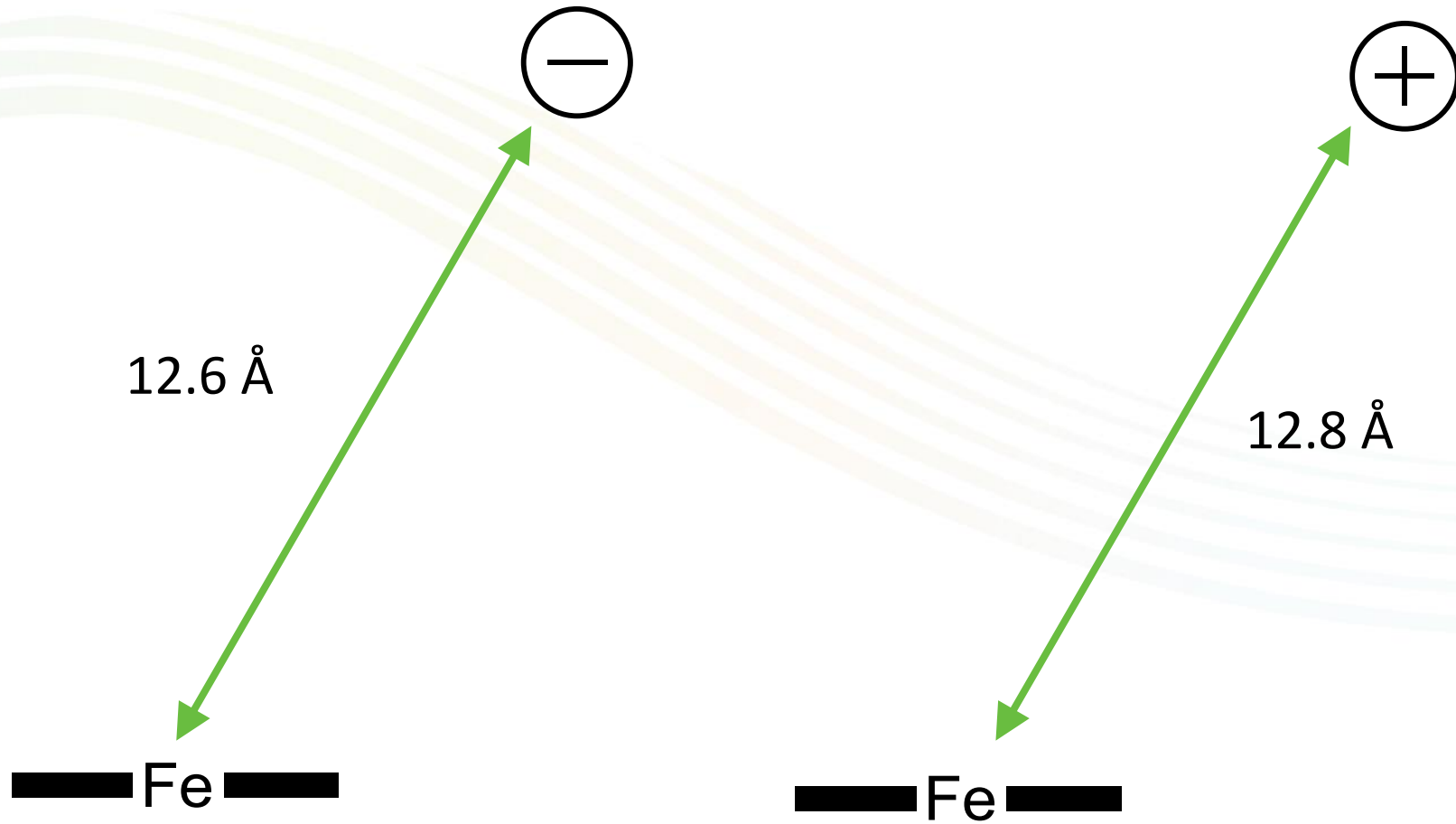
CYP 2D6

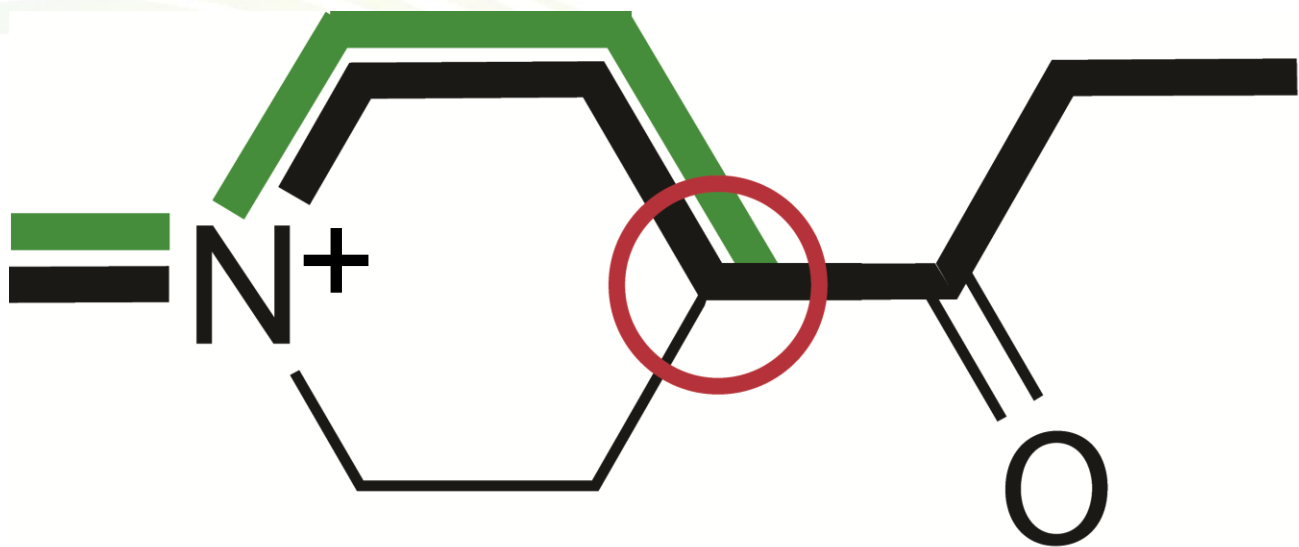


CYP 2C9



CYP2D6 vs. CYP2C9



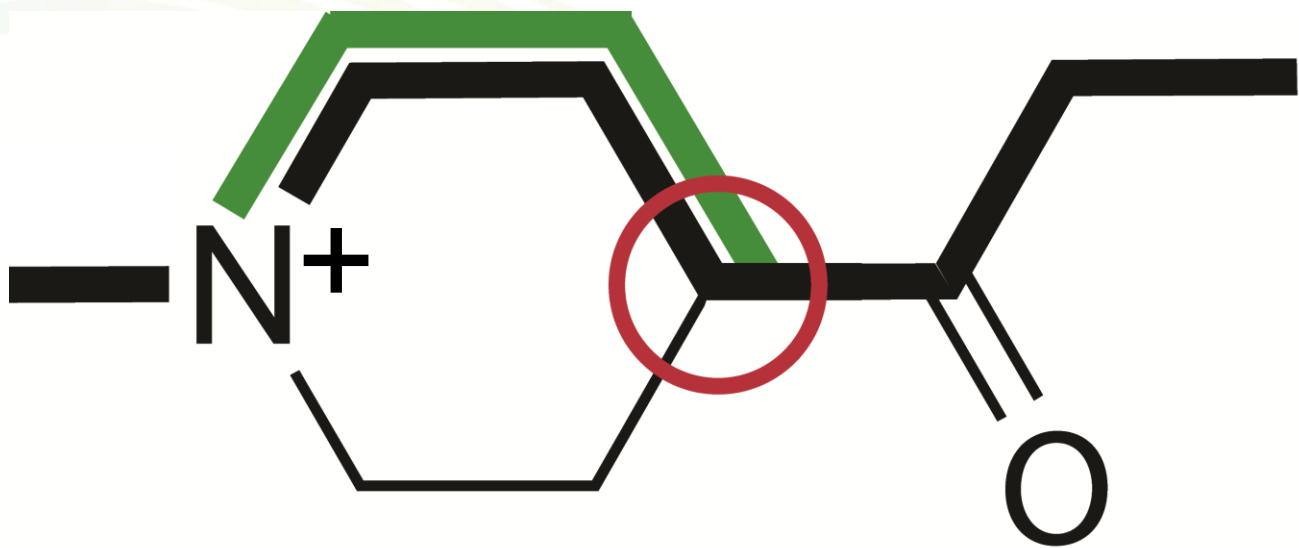


Relative Span

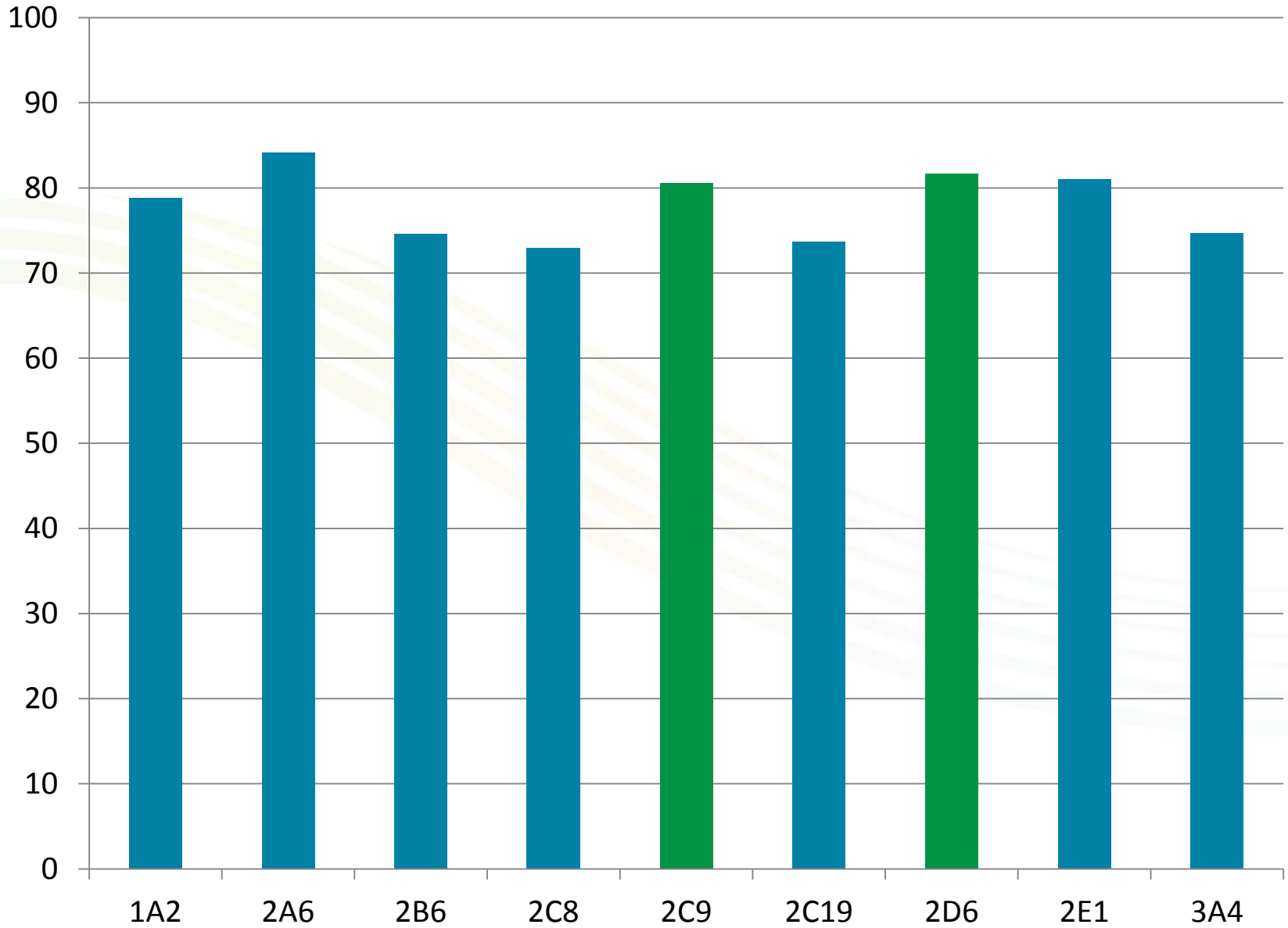
$$4 / 7 = 0.57$$

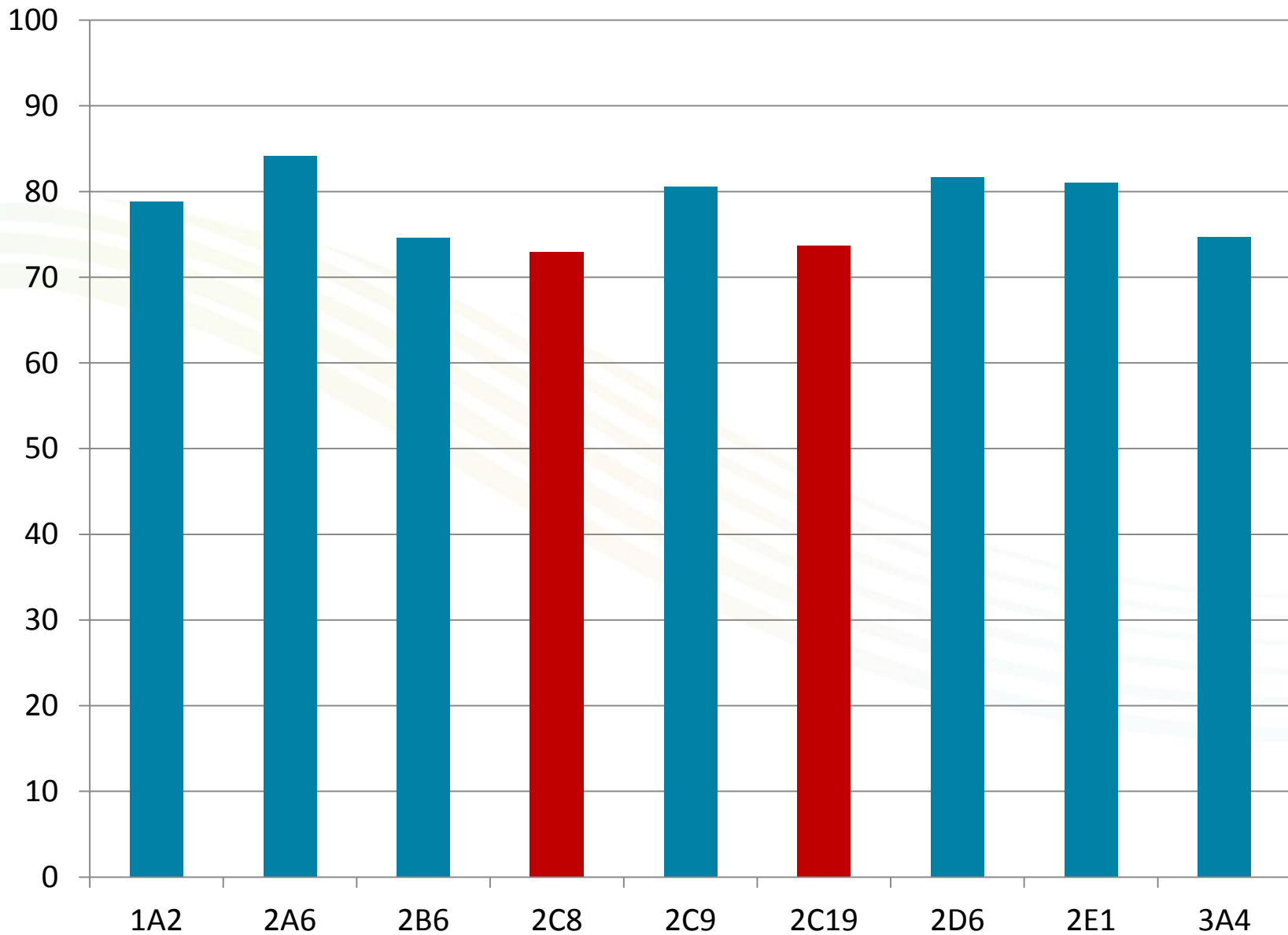
Span2End

$$7 - 4 = 3$$

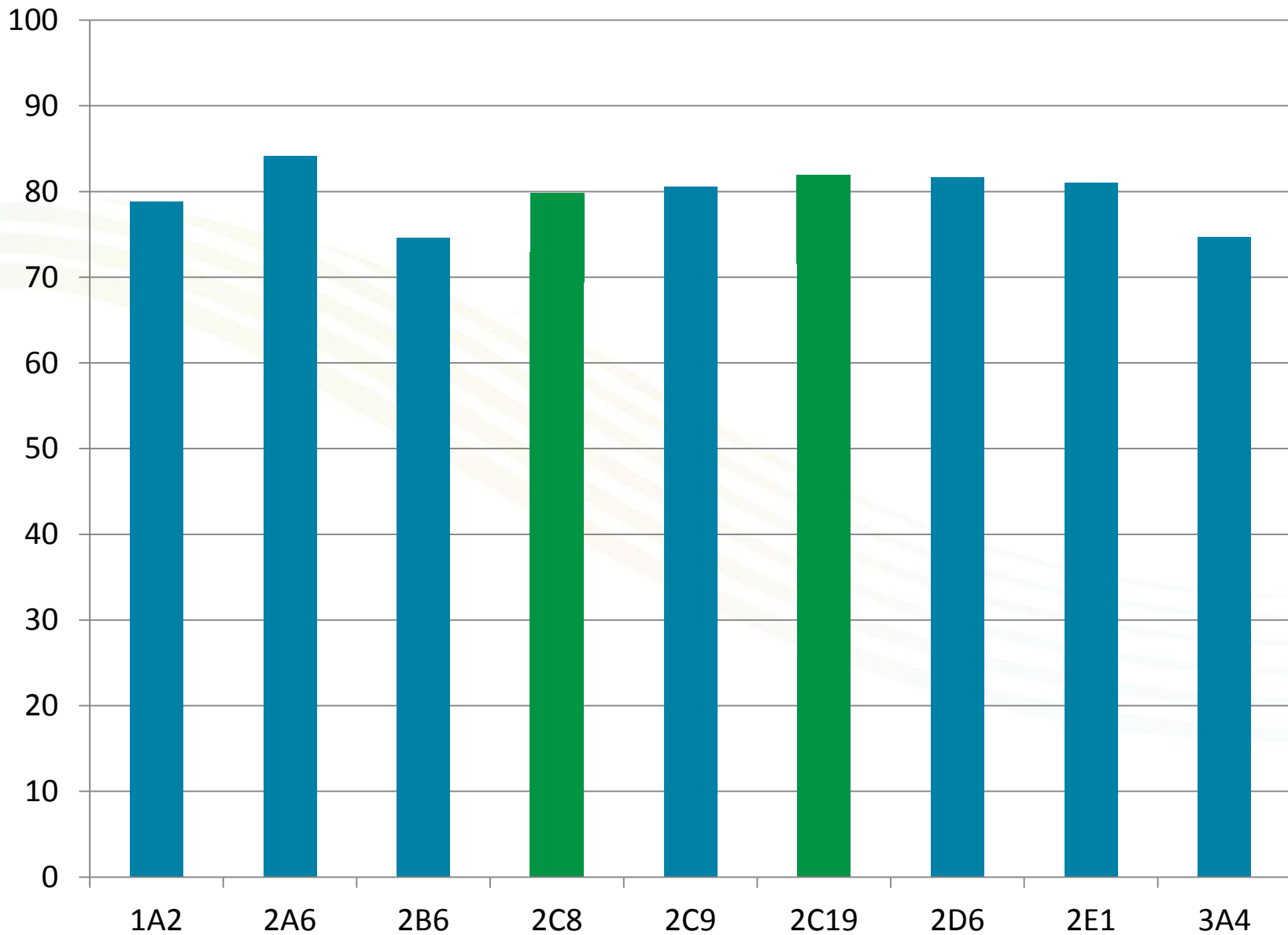


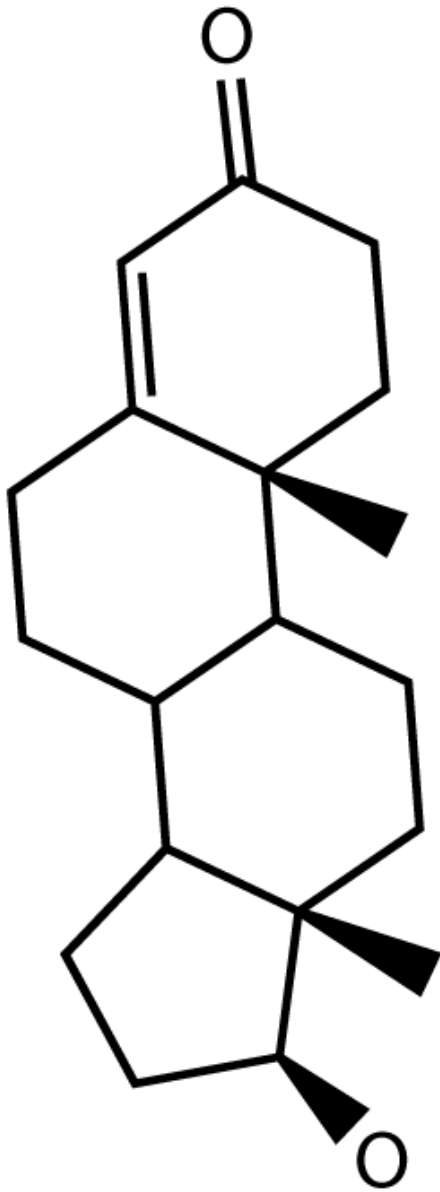
N⁺dist
3



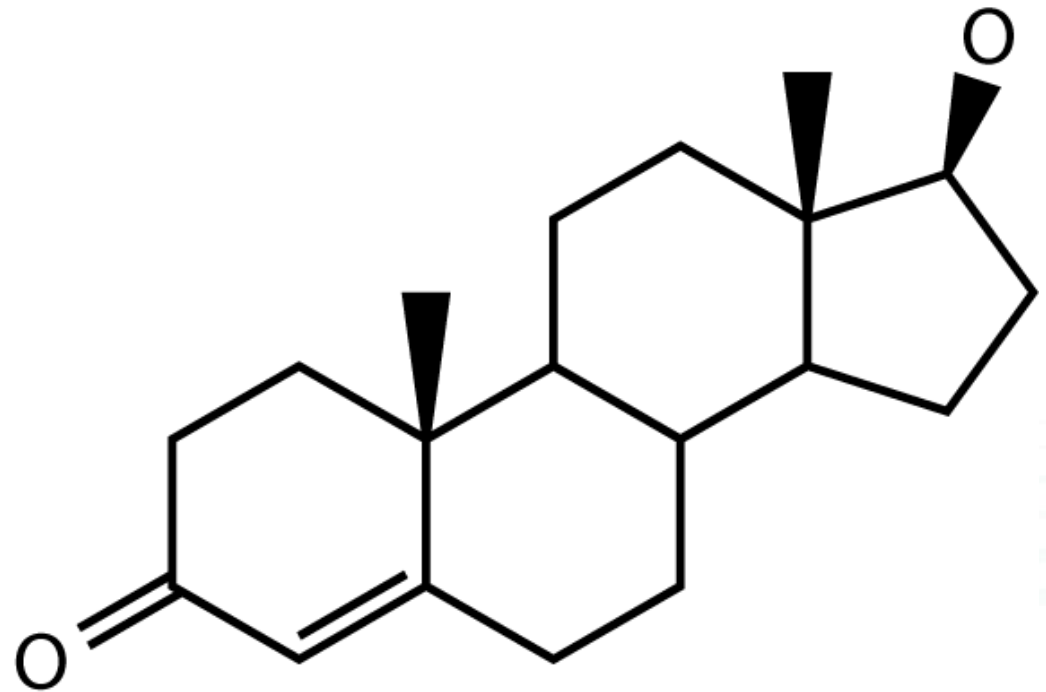


$2C9=2C8=2C19?$

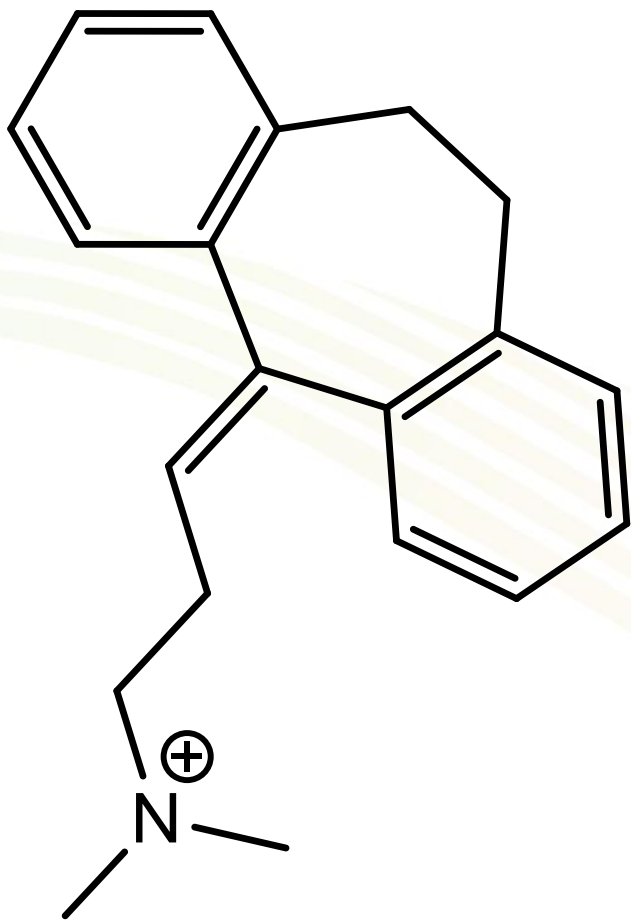




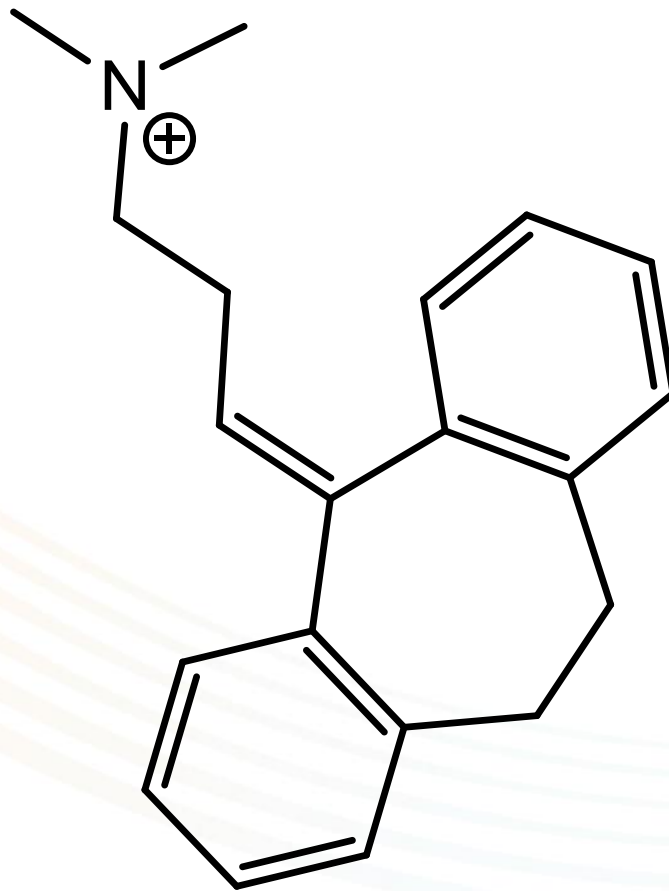
Fe



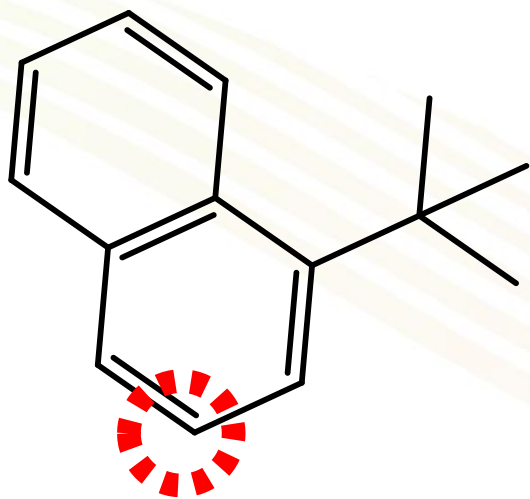
Fe



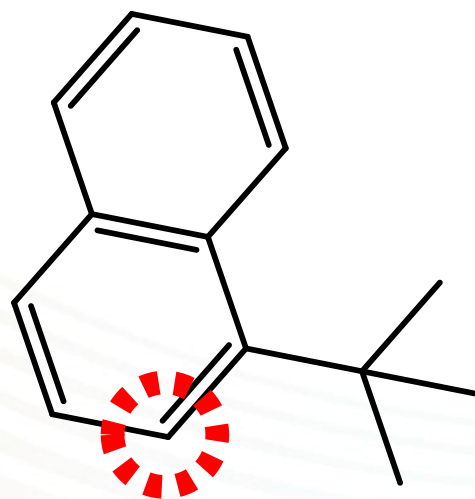
— Fe —



— Fe —

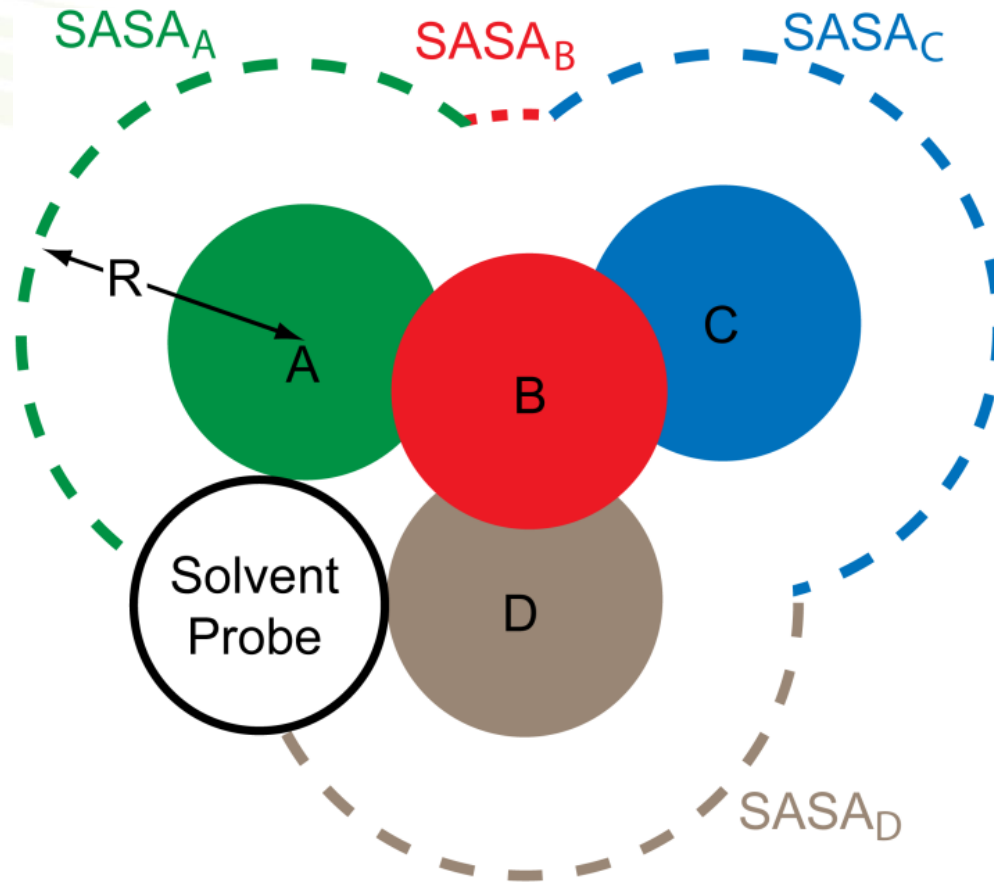


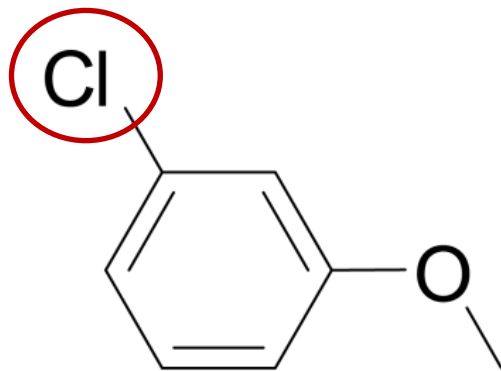
— Fe —



— Fe —

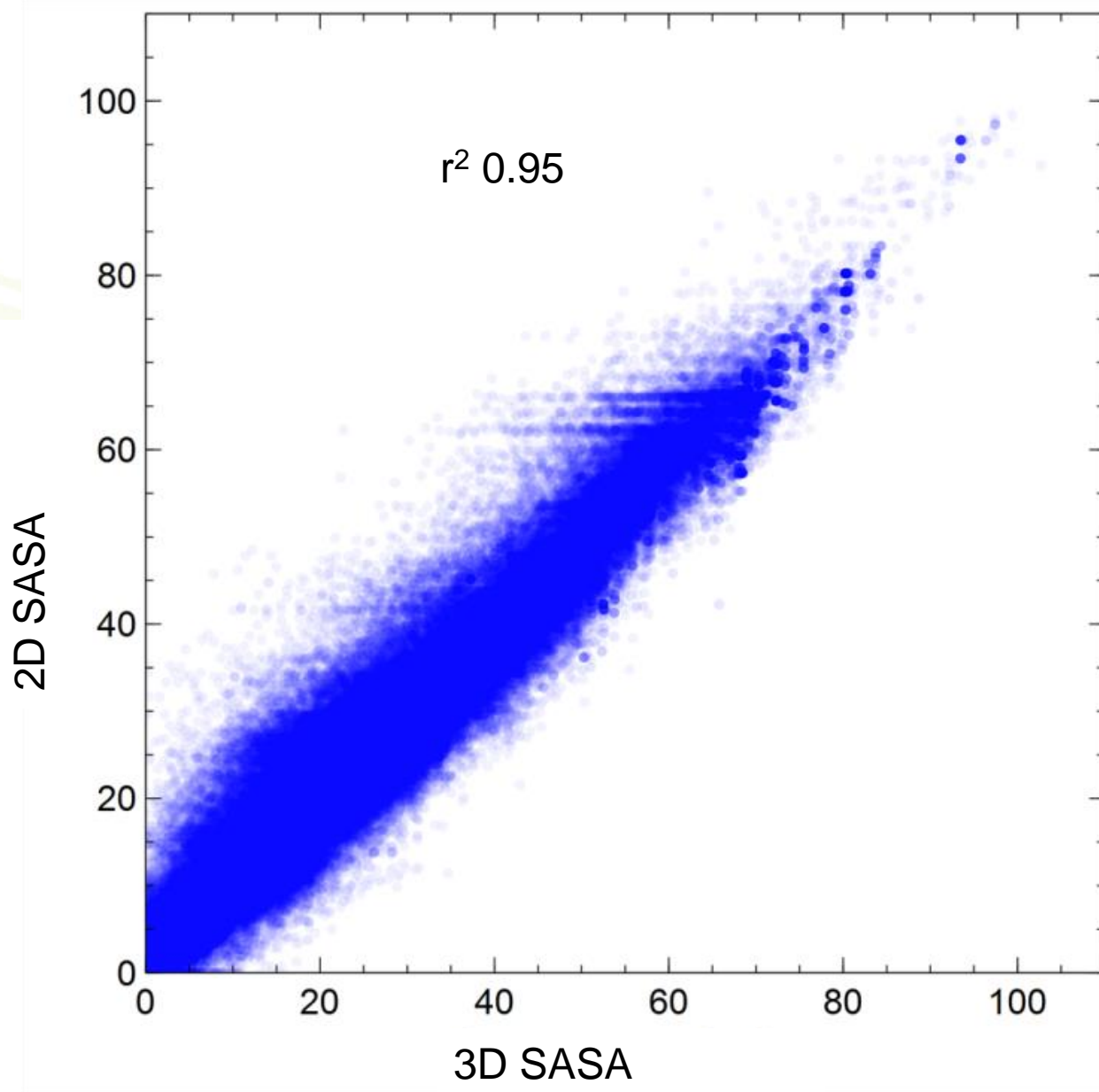
Solvent Accessible Surface Area

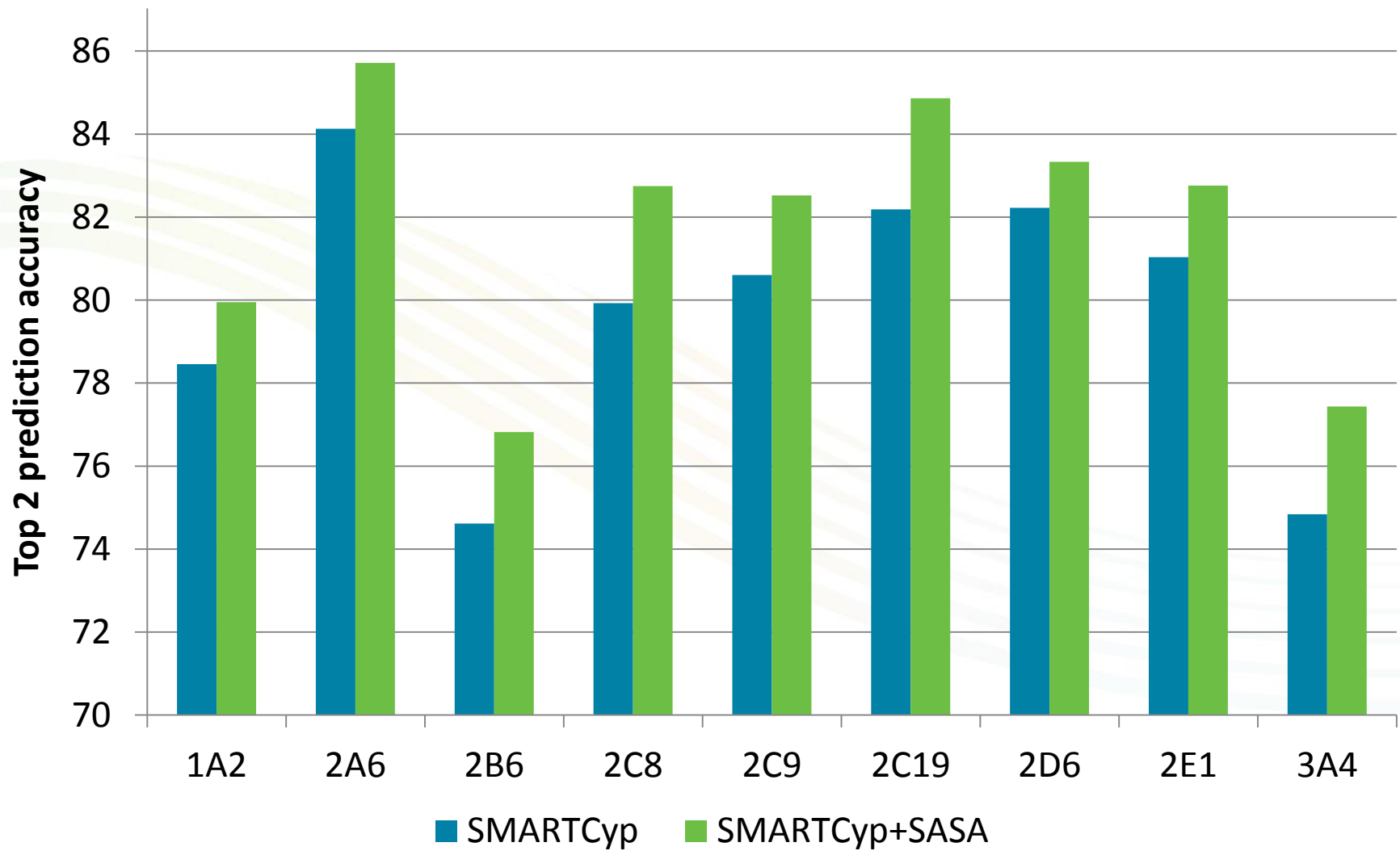




Cl C.ar O.3 C.3

	Level 0	1		
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Rydberg et al., Mol. Pharmaceutics, 2013, 10, 1216-1222

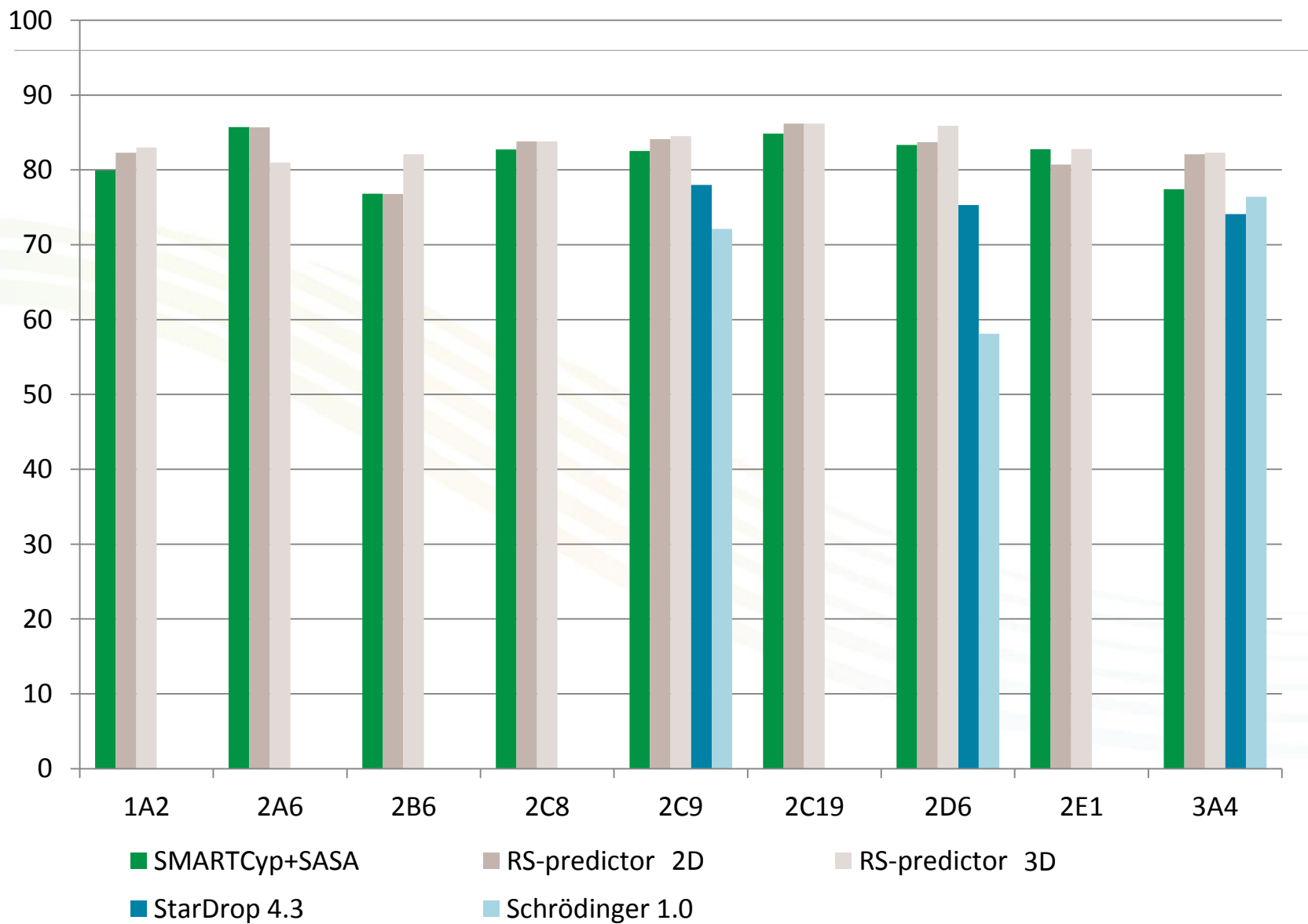

$$\text{Score} = \text{Reactivity} - 8 * \text{Accessibility} - 0.04 * \text{SASA}$$

86% **7%** **8%**

Score = Reactivity – Parmacophore – Span2End – 0.04*SASA

2C9 **64%** **7%** **25%** **4%**

2D6 **51%** **37%** **10%** **2%**



www.farma.ku.dk/smartcyp



Acknowledgements

University of Copenhagen, Denmark

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Lhasa Ltd.

Alfred Benzon Foundation

Danish Council for Independent Research

Olle Engqvist Byggmästare Foundation

New P450 Research at Optibrium

Part of HeCaToS European consortium - €12M FP7 grant

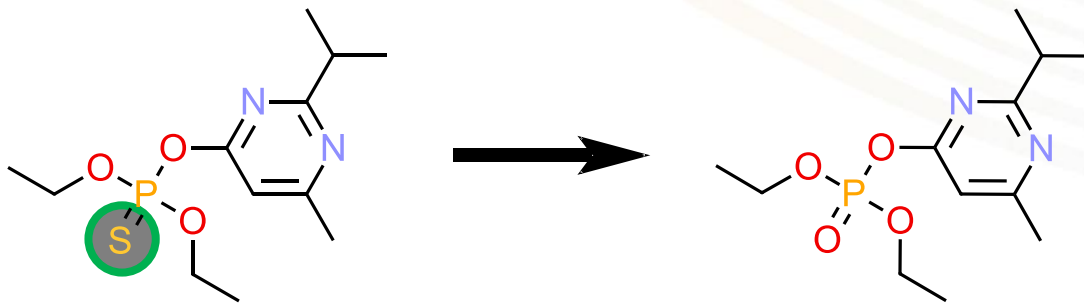
- Systems for prediction of hepatic and cardiac toxicity
- 5 year project
- Ranging from clinical data gathering to computational research

Optibrium contribution – Prediction of P450 metabolism and bioactivation

Future StarDrop developments

New Reaction Mechanisms:

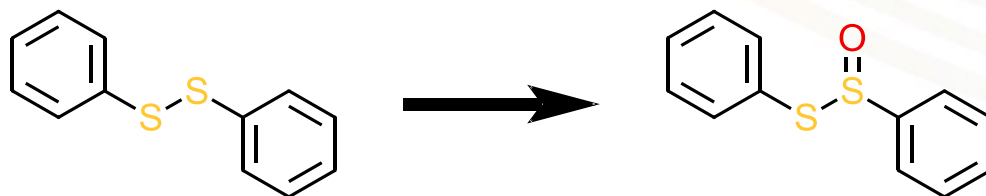
Desulfurization of phosphothioates



Future StarDrop developments

New Reaction Mechanisms:

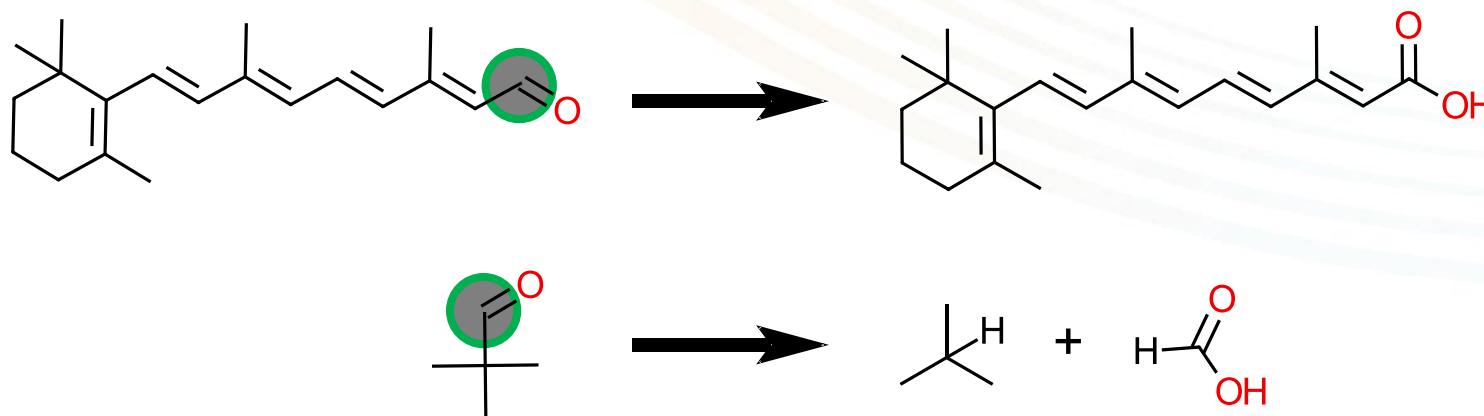
Oxidation of disulfides



Future StarDrop developments

New Reaction Mechanisms:

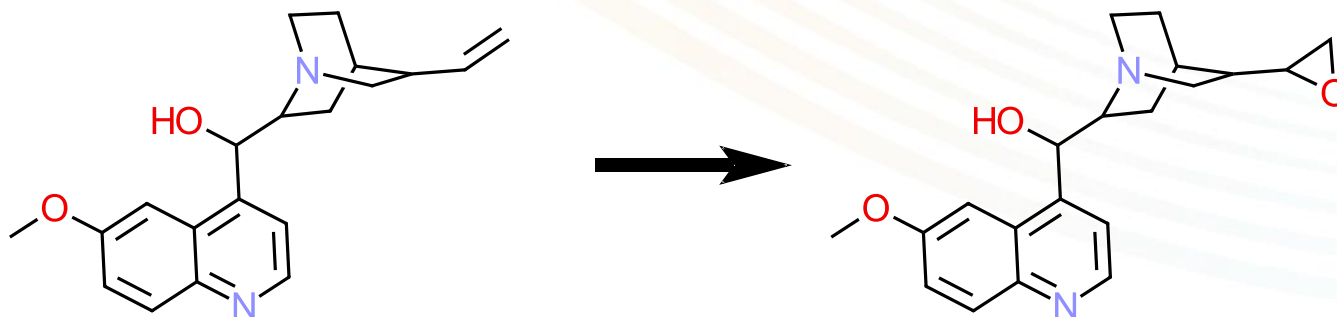
Aldehyde oxidation/deformylation



Future StarDrop developments

New Reaction Mechanisms:

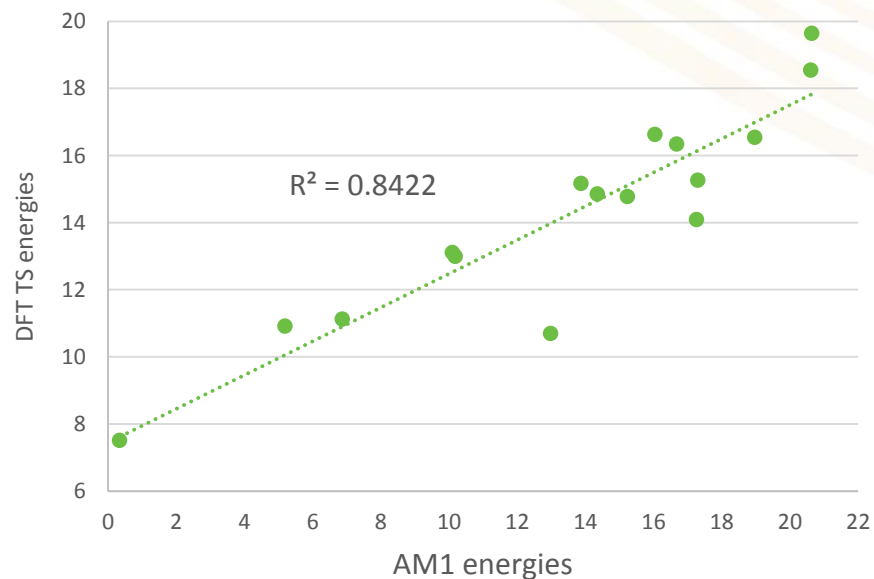
Epoxidations



Future StarDrop developments

New Reaction Mechanisms:

Epoxidations



Future StarDrop developments

Extend P450 models to other isoforms

1A1, 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, 3A4, 3A5

Build isoform selection models

Add metabolite formation

Estimate reactivity of formed metabolites

Prediction of toxicity due to reactive metabolite formation