

# Exploiting In Silico Techniques for Human Phase I Metabolism Prediction with Smartphone

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A **xenobiotic** is a chemical which is found in an organism but which is not normally produced or expected to be present in it



## How does the body protect itself against xenobiotics ?

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- *By preventing xenobiotics from entering into the bloodstream or organs*

Absorption or  
Distribution

- *By physical elimination*

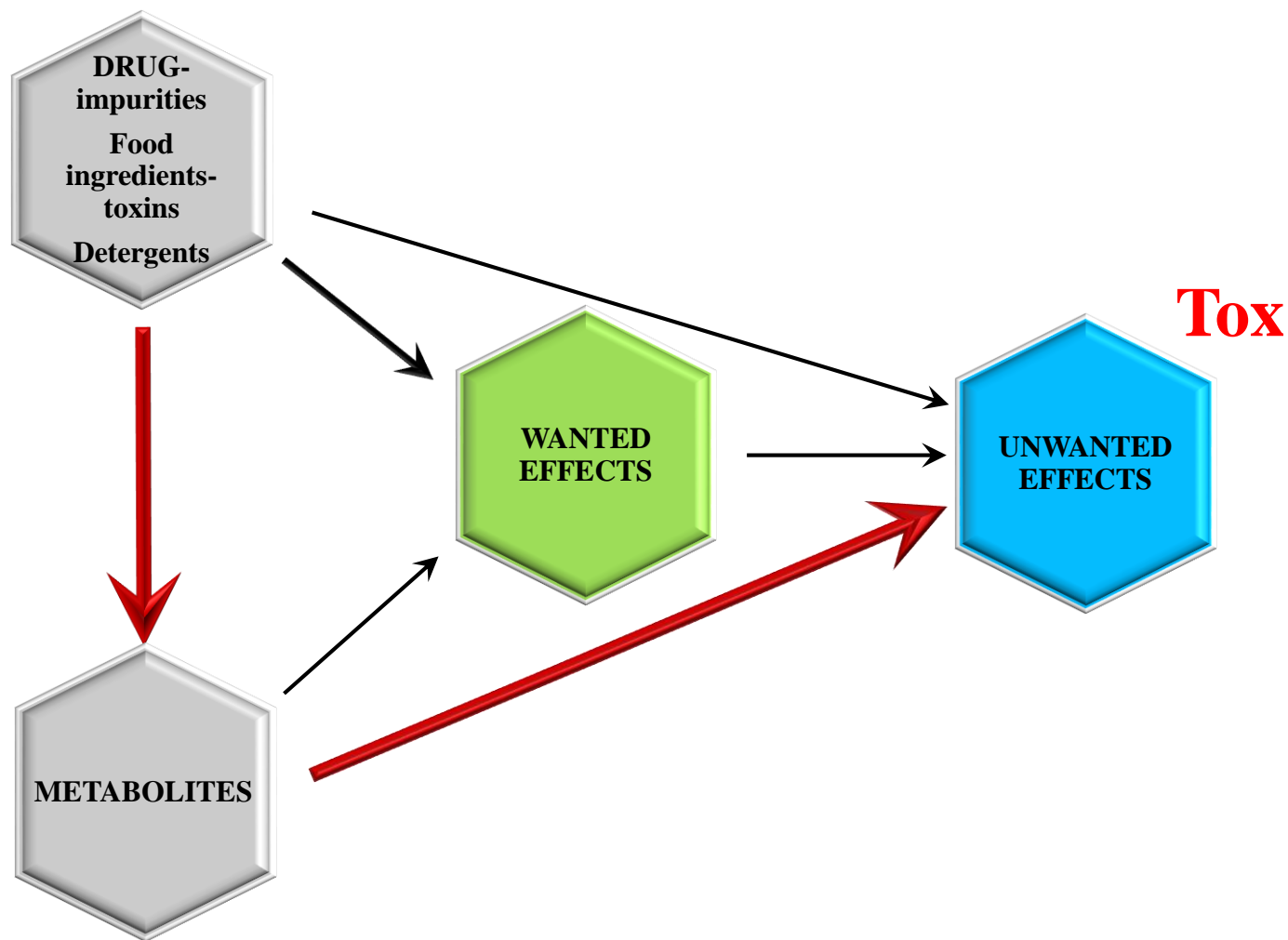
Excretion

- *By chemical elimination*

Metabolism =  
biotransformation

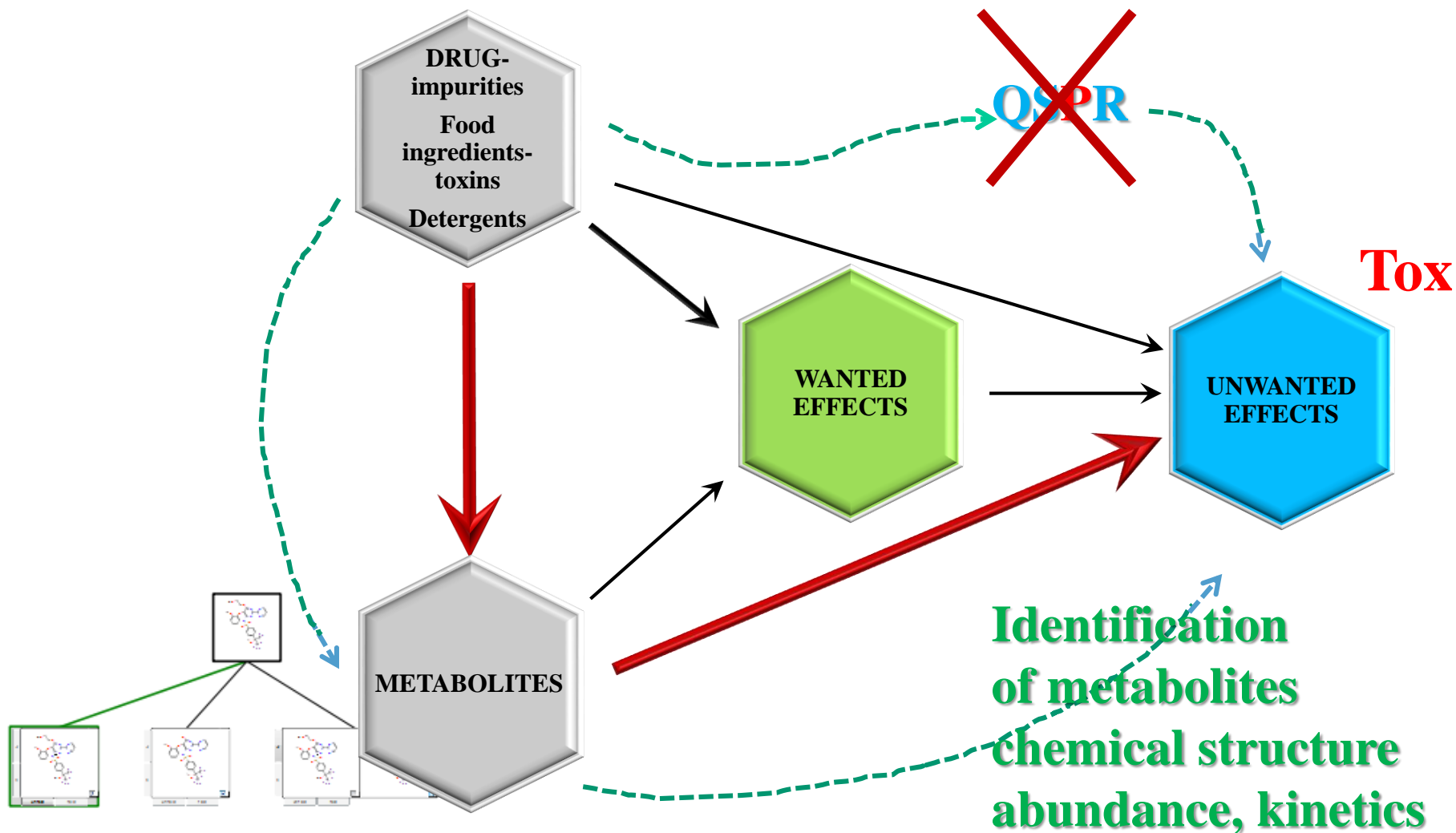


*The xenobiotic is transformed in the body into products (metabolites) which are usually more water-soluble and easier to excrete.*



**Chemical description**  
**01100011100010101**

**ADMe**

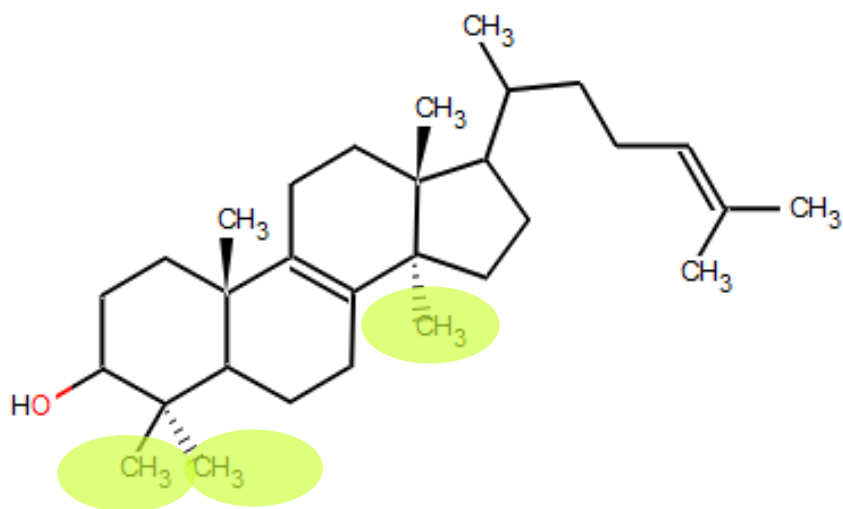


# P450 enzymes are not new entities in organic synthesis

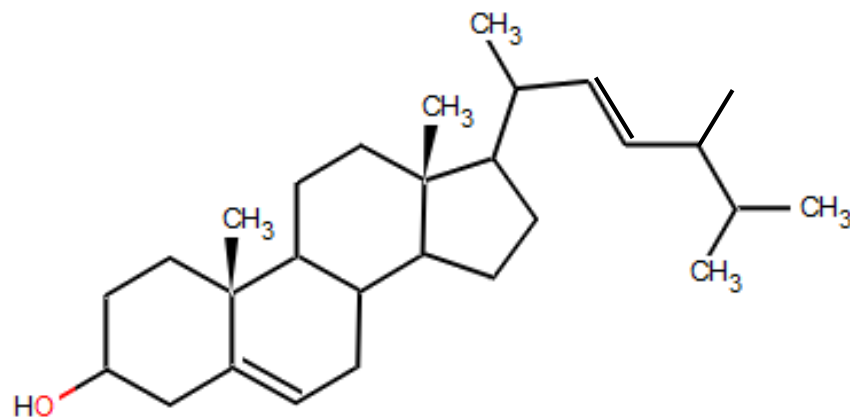
## Example:

in sterol biosynthesis P450 can oxidise unreactive methyl groups in the presence of double bonds

Lanosterol



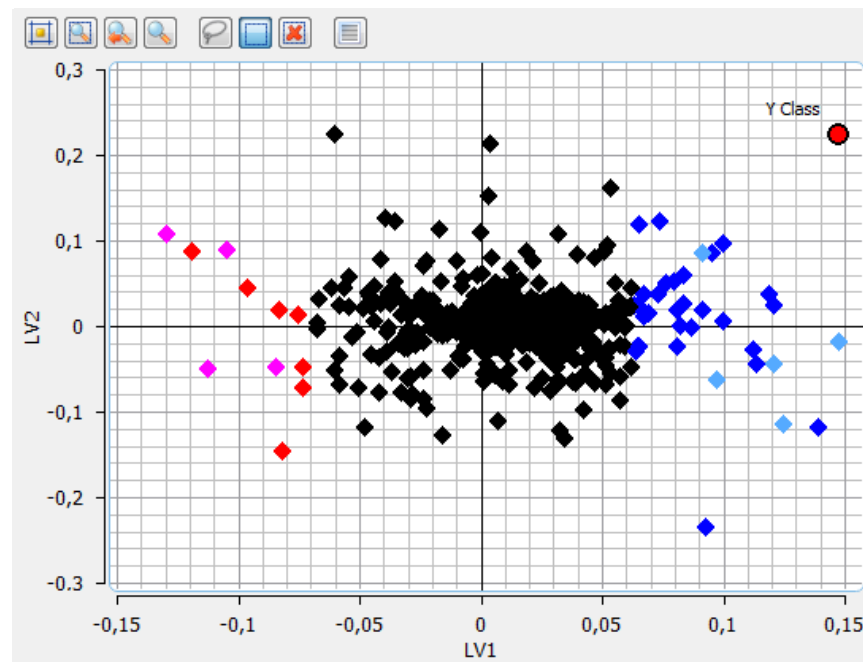
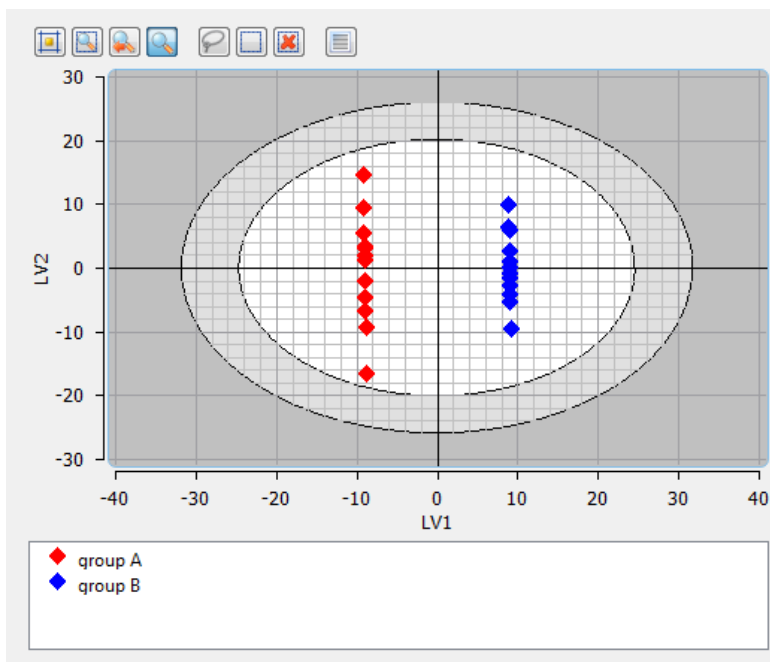
Ergosterol conversion



# Metabolomics/lipidomics signal interpretation

**WARNINGS**

**TOO GOOD!...DRUG METABOLITES EFFECT  
(lipid impairment associated to drugs)**



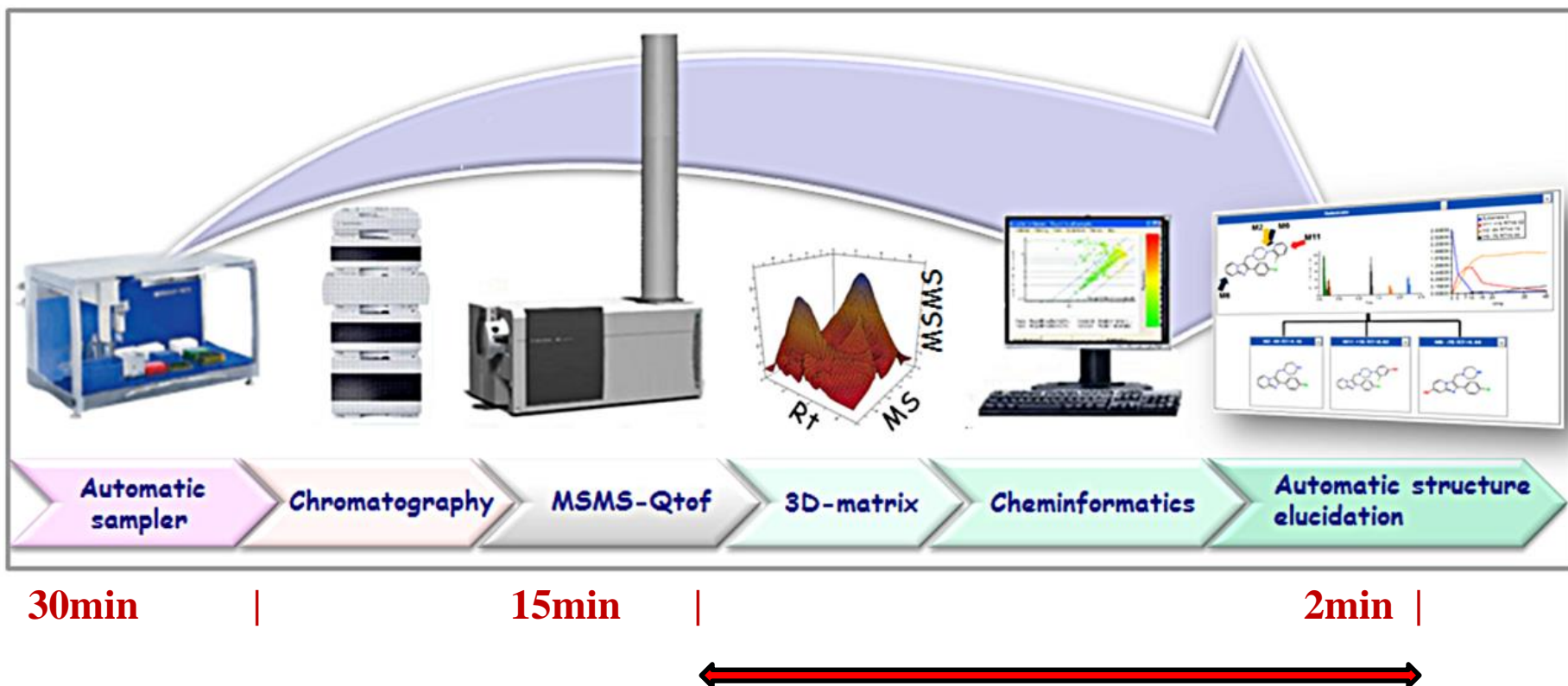
**METAB DRUG 1**

**METAB DRUG 2**

**DEDICATED SOFTWARES FOR UNTARGETED LIPIDOMICS**

# Today MetID – the *HITROXEN* approach

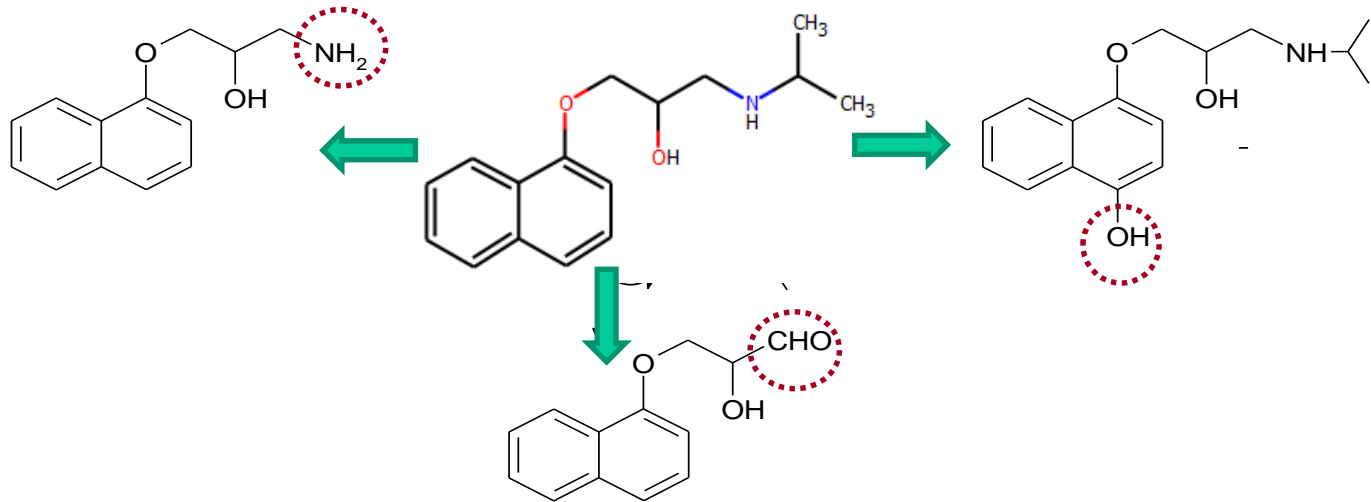
## Semi-automatised procedure for MetID profiling



**Full MetID - 20 compounds/day (report included)**

Propranolol -> several metabolites

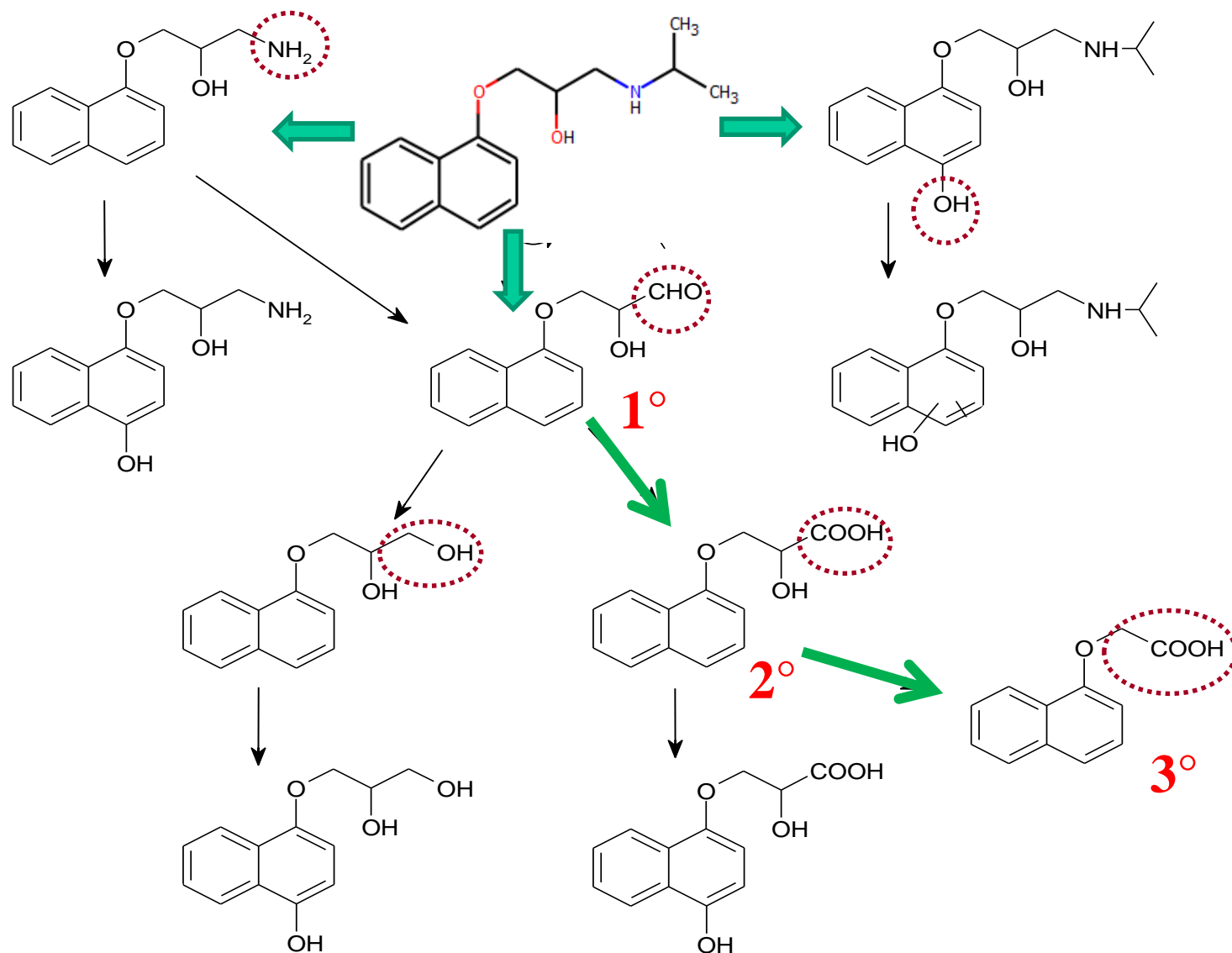
## Phase I & II metabolism



Phase I metabolism by CYPs

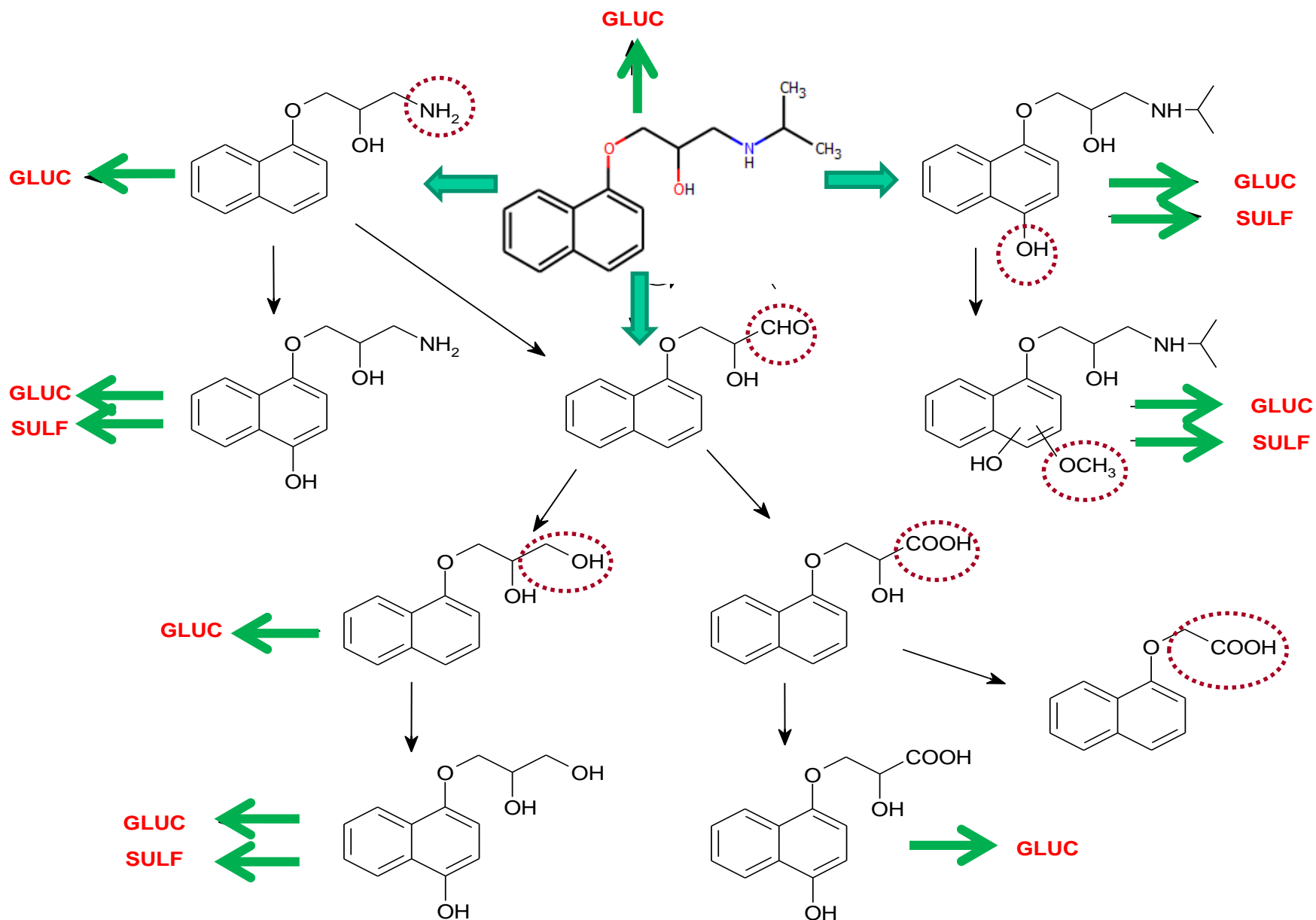
Propranolol -> several metabolites

# Phase I & II metabolism

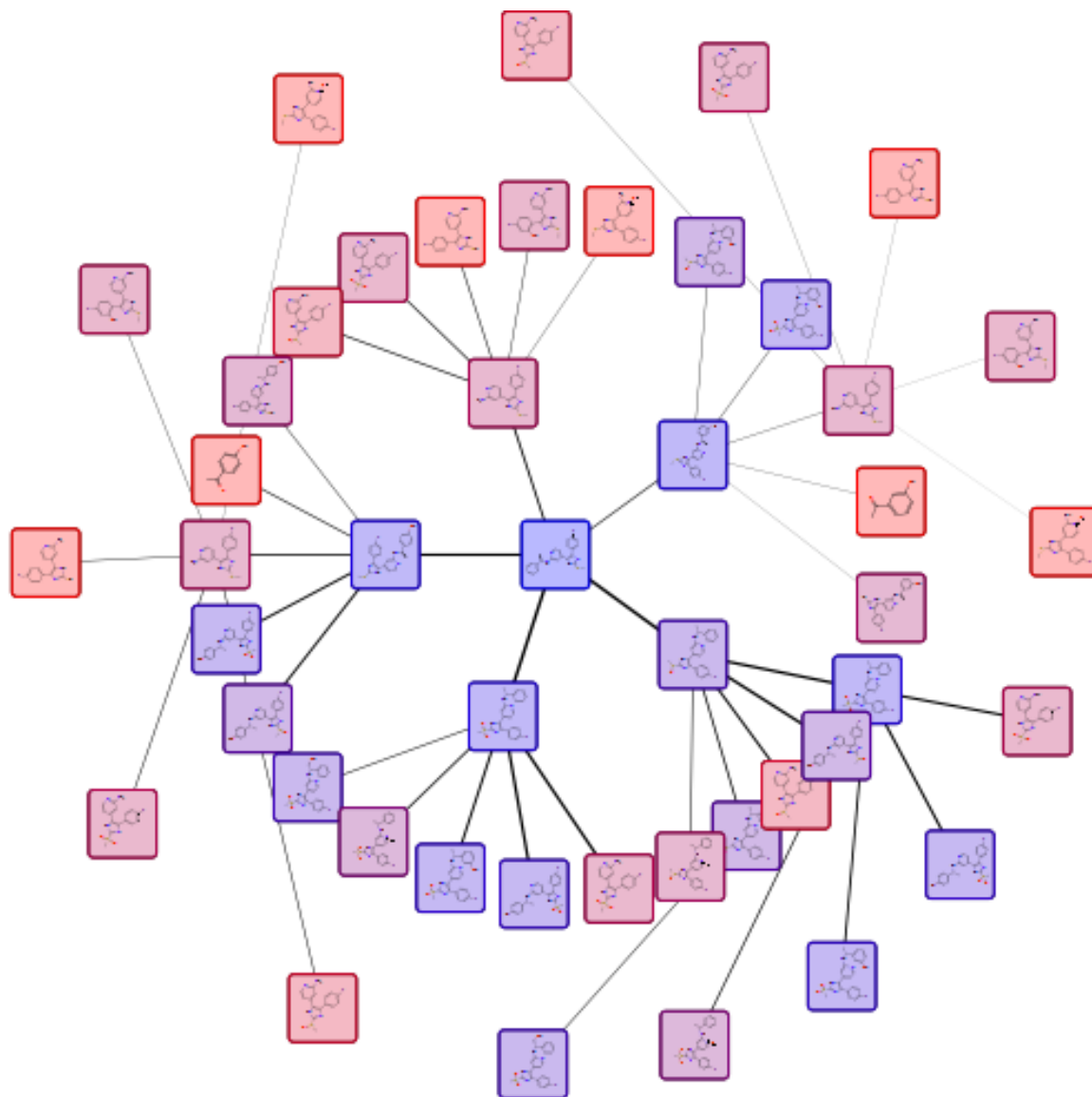


Propranolol -> 21 metabolites

# Phase I & II metabolism



**P450**  
**FMO**  
**AOX**

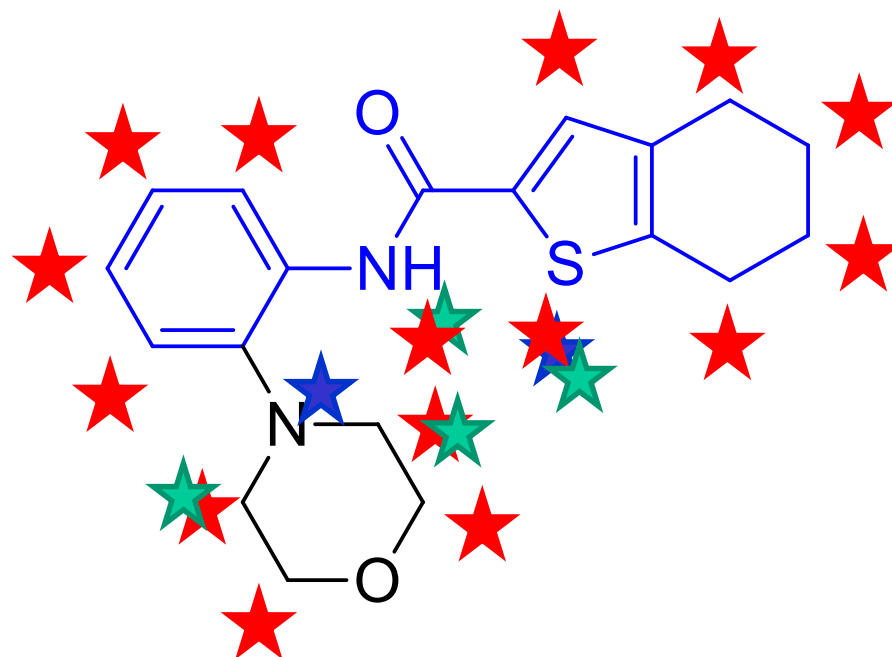


**Biotransformations (*in silico*) of ML3403**

P450

FMO

AOX

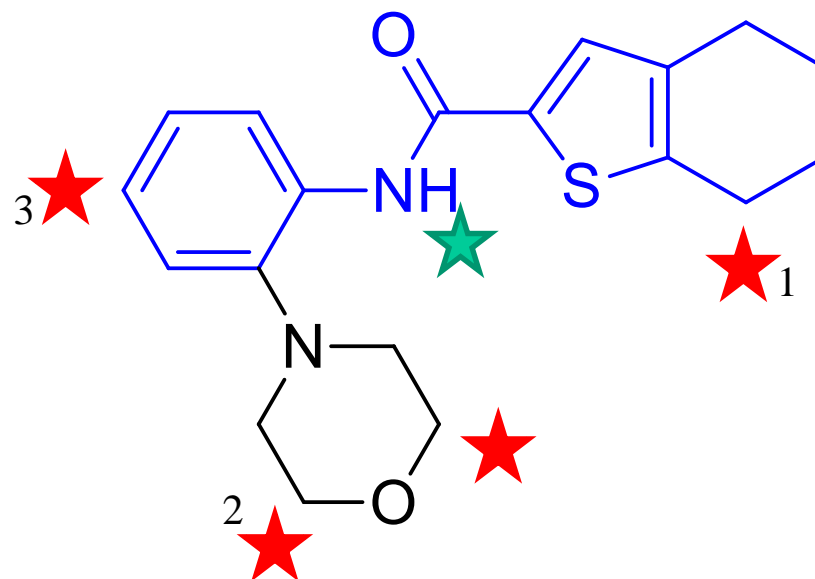


**Potential biotransformations (*in silico*) of MC041**

**P450**

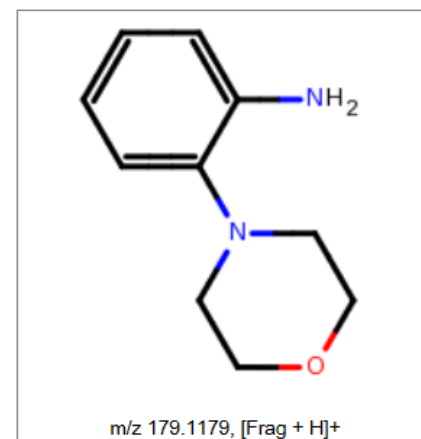
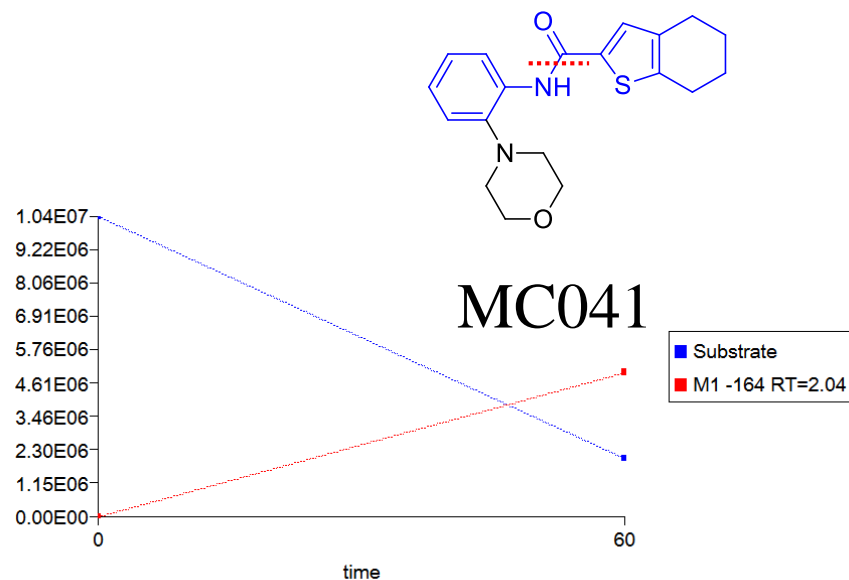
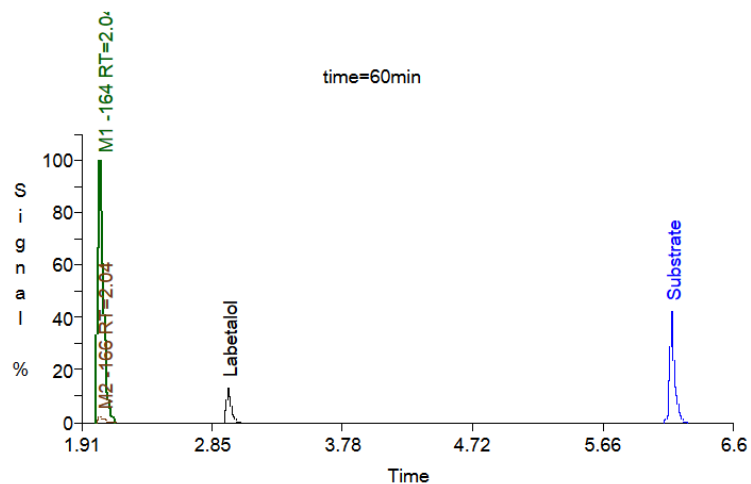
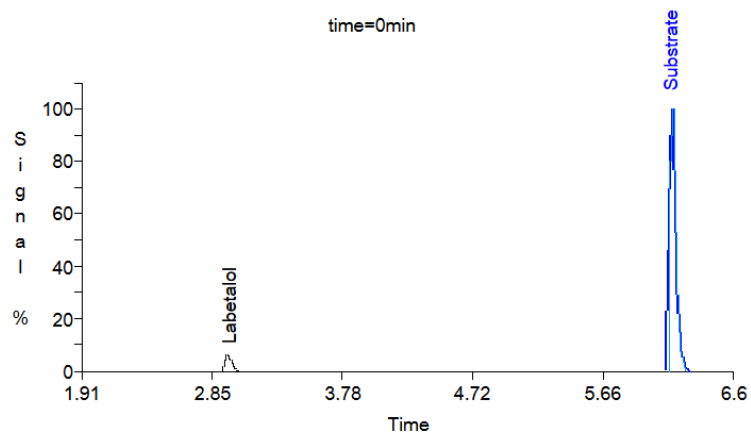
**FMO**

**AOX**



**Exp. biotransformations (*in silico*) of MC041**

# Metabolism of MC041



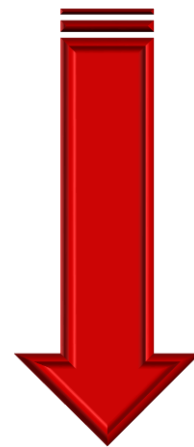
Exposure contribution

Reactivity contribution

$$P_{\text{SoMi}} = [(1+w_e) \cdot Ei] \cdot [(1+w_r) \cdot Ri]$$

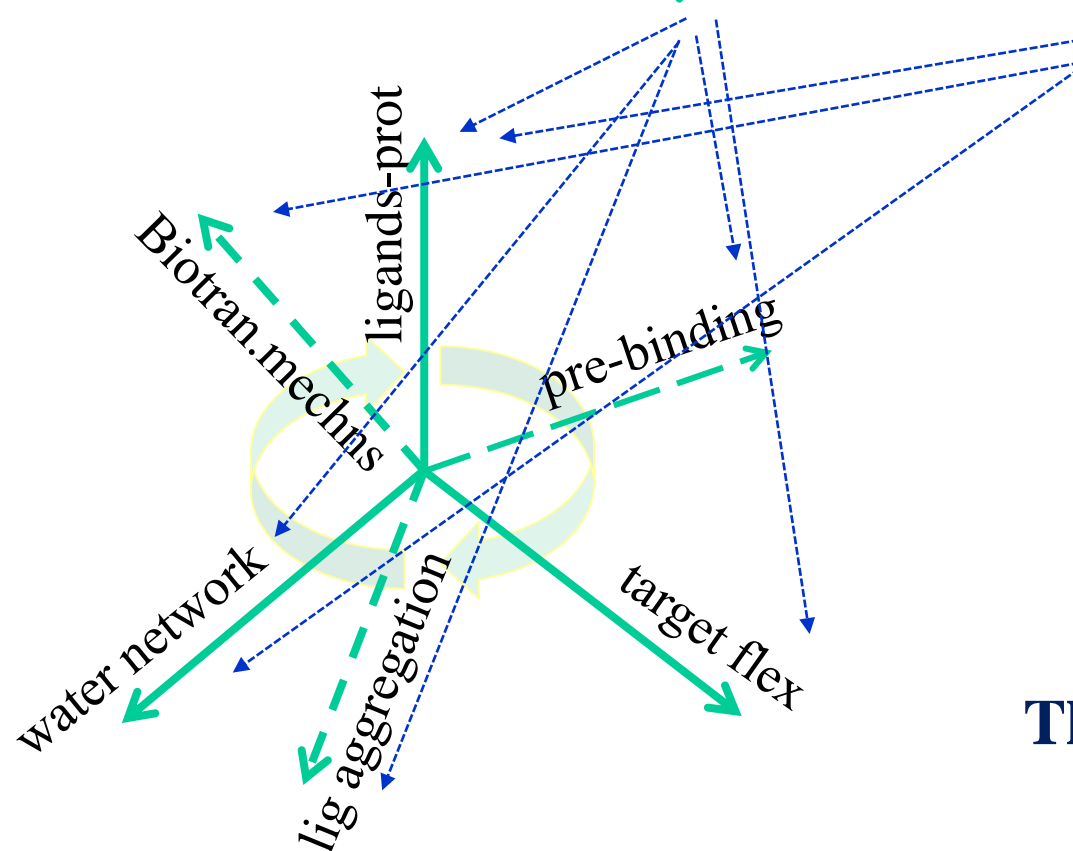


Exposure of  
reactive atom to  
reactive center  
Heme, FAD, Mo  
Cu++ .....



Atom reactivity  
(RAE, nucleofilicity,  
electrofilicity ...)

$$P_{\text{SoM},i} = \underbrace{(1 + w_e)E_i}_{\text{green}} \underbrace{(1 + w_r)R_i}_{\text{red}}$$



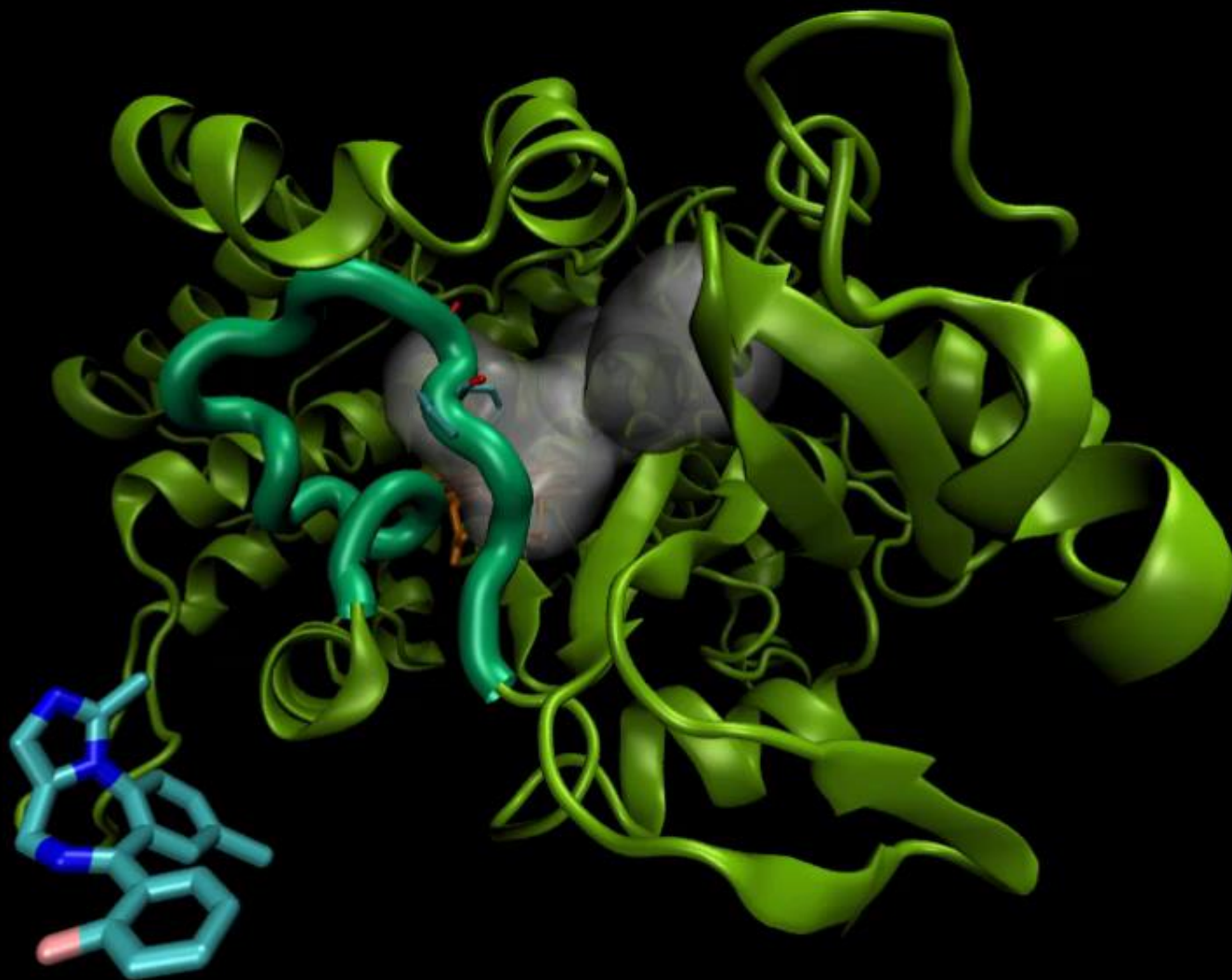
**The growing complexity**

**Holistic approach**

Not 6-dimensional ... but still dimensionally demanding

1tqn *holo*  
16000 wat  
35 wat

30 ns  
6 weeks GPU



## MetaSite 5.0

*New reactivity and exposure integrated*

*Results (on compounds with well-known metabolite ranking)*

*st. validation method  
(top three solutions)*

*new validation method  
(precise ranking)*

*98% correct solutions*

*2D6*

*80% correct solutions*

*96% correct solutions*

*2C9*

*78% correct solutions*

*94% correct solutions*

*3A4*

*75% correct solutions*

# MetaSite 5.0

*Results (on compounds with well-known metabolite ranking)*

*st. validation method  
(top three solutions)*

*new validation method  
(precise ranking)*

*100% correct solutions*

*FMO*

*95% correct solutions*

*100% correct solutions*

*AOX*

*95% correct solutions*

*Substrate selectivity*

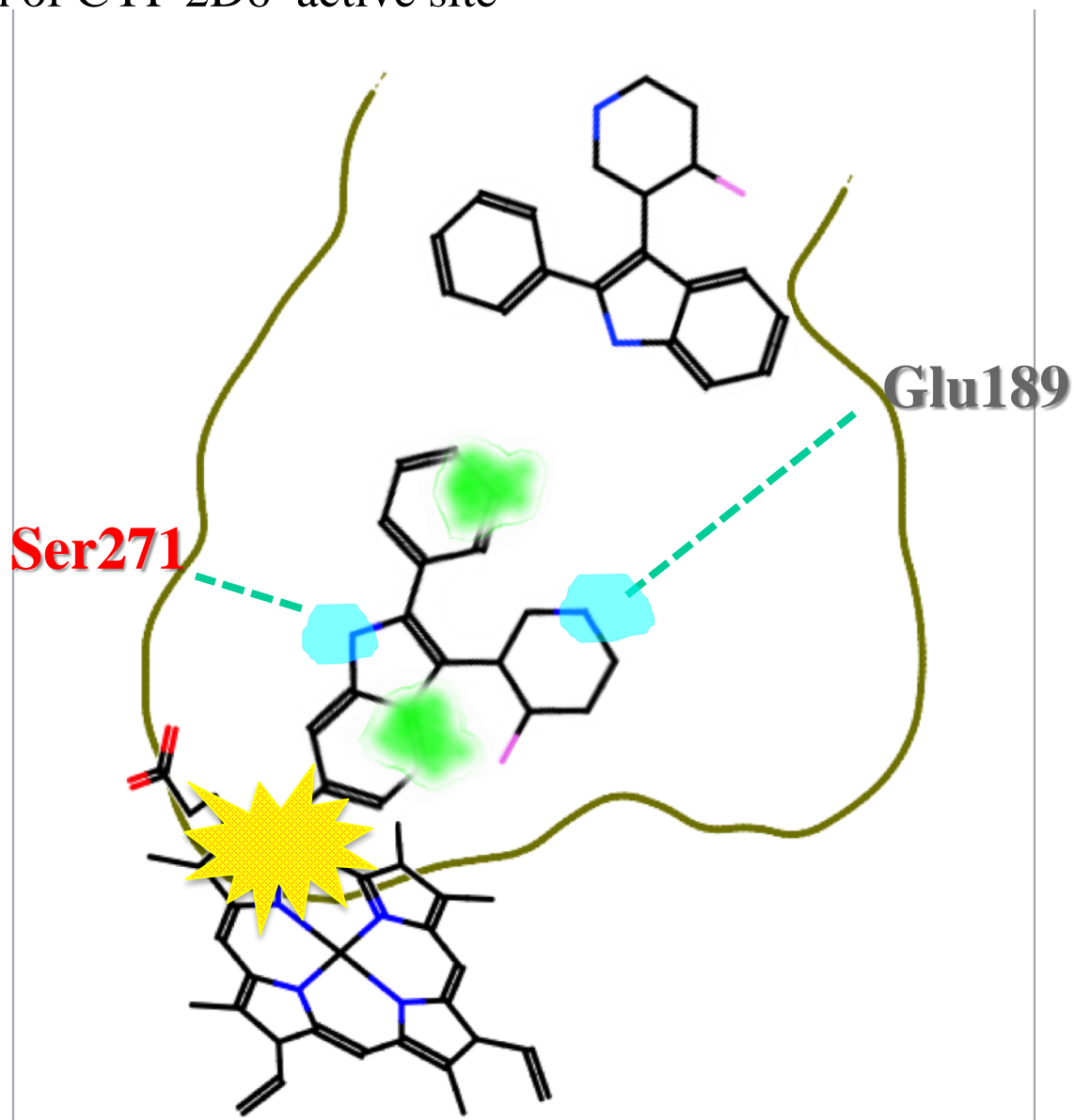
*82% correct solutions*

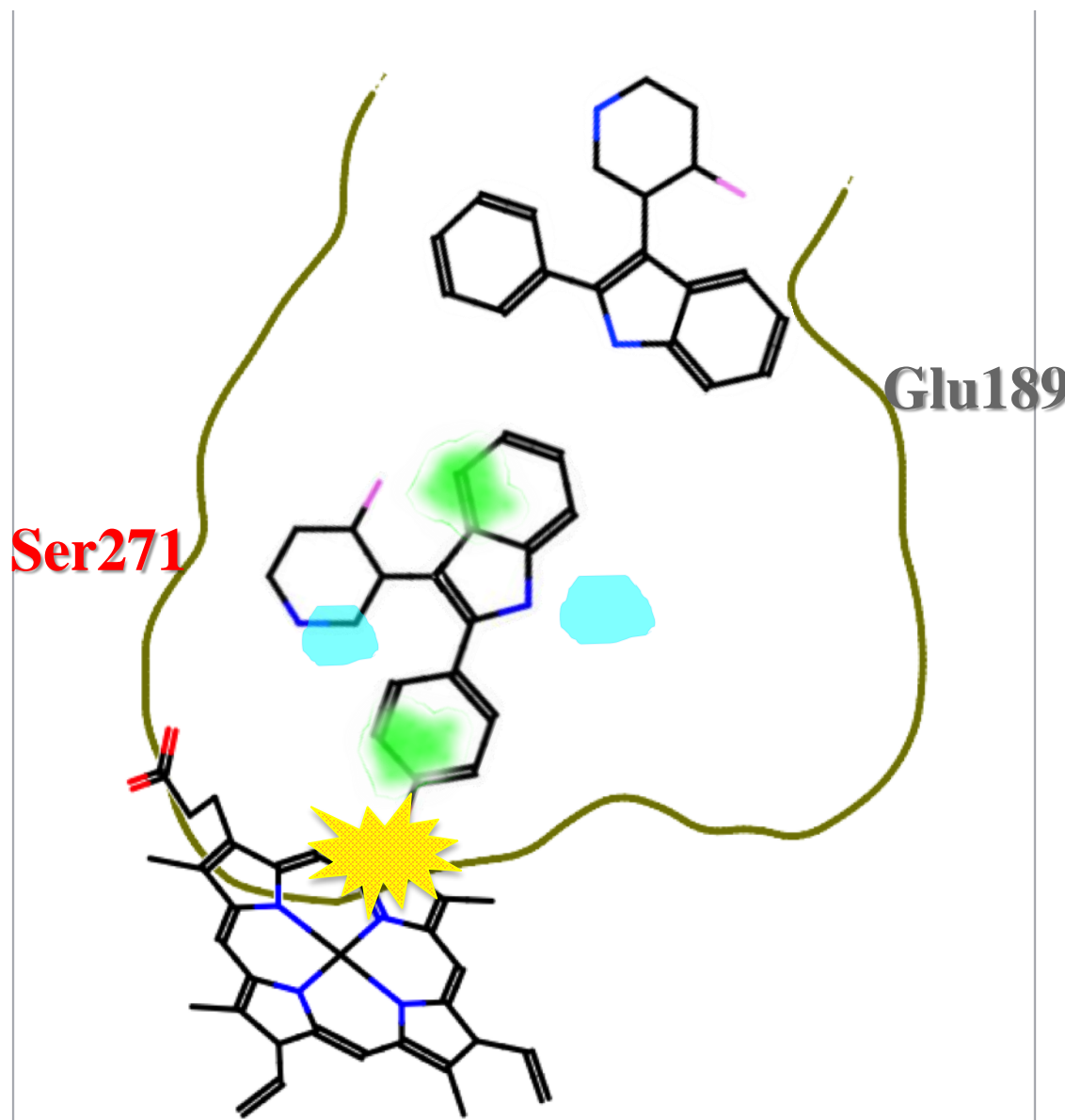
*FMO*

*85% correct solutions*

*AOX*

## 2D representation of CYP 2D6 active site

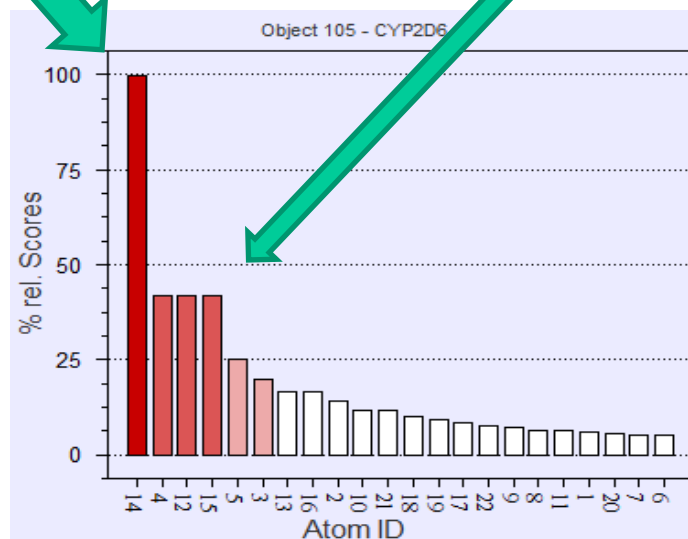
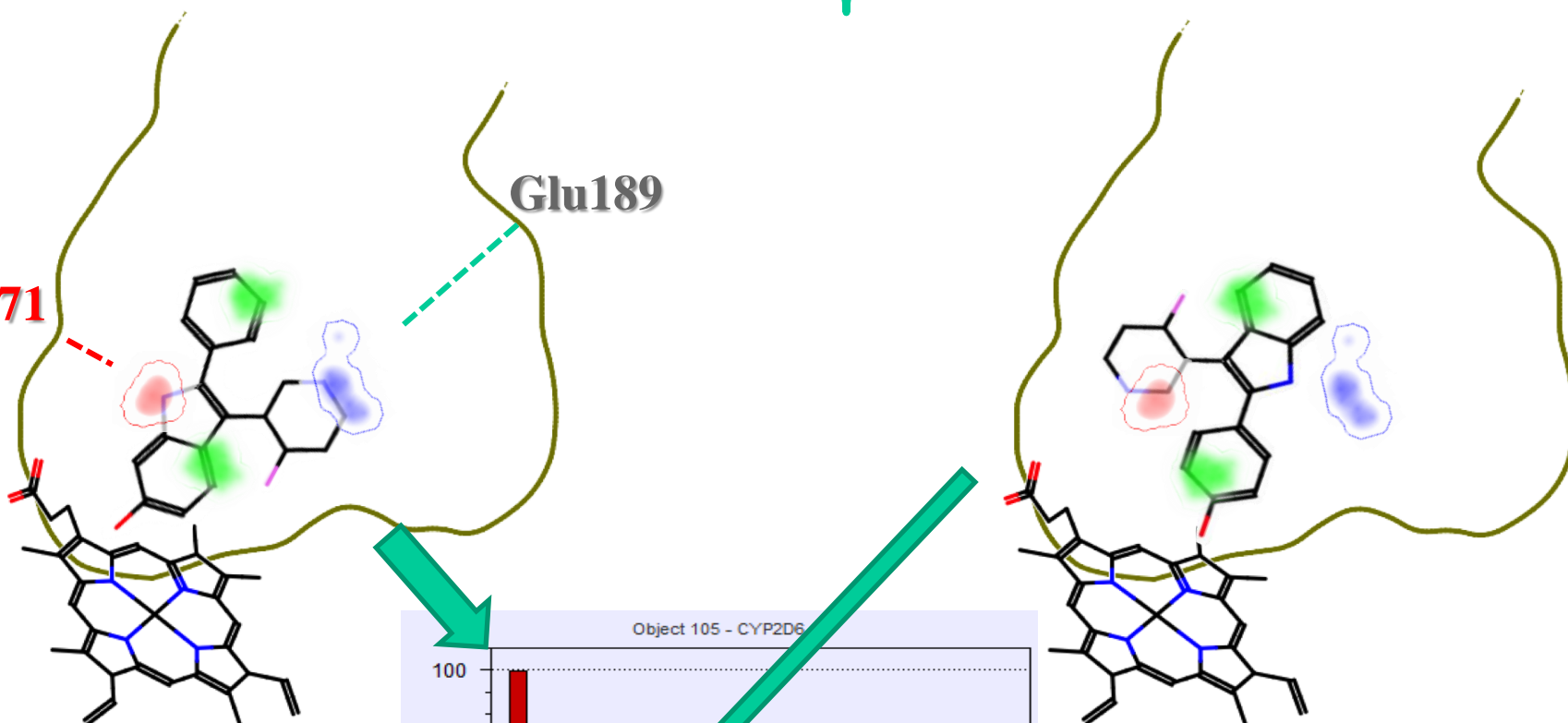




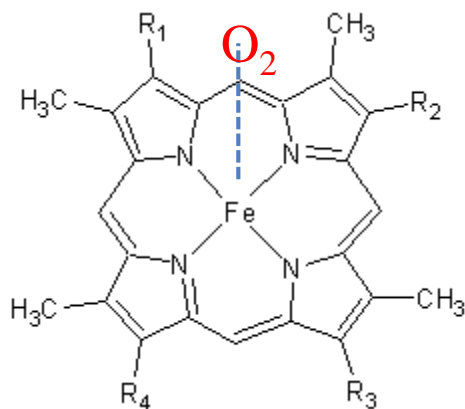
$$P_{\text{SoM},i} = \underbrace{(1 + w_e)}_{\text{Electrostatic}} E_i (1 + w_r) R_i$$

Ser271

Glu189

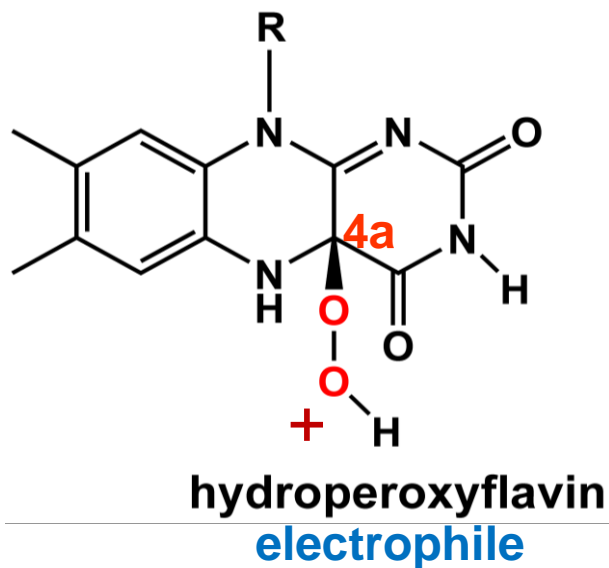


## CYP450

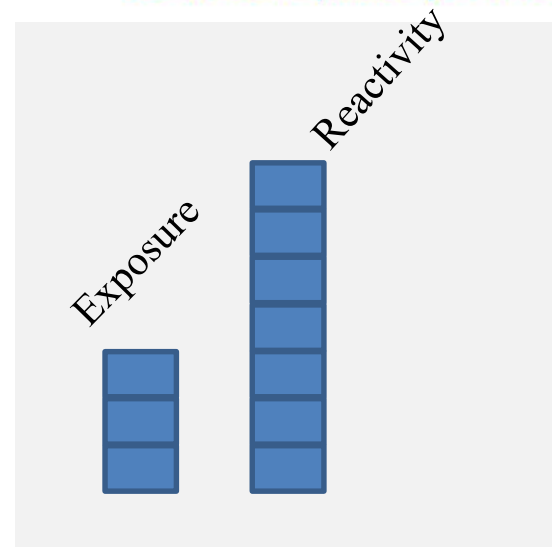
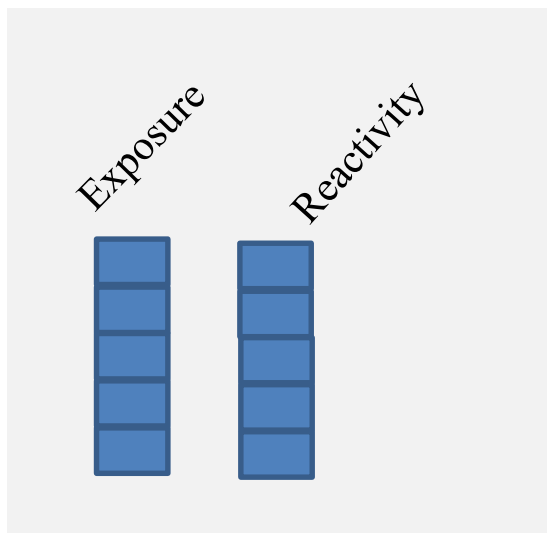
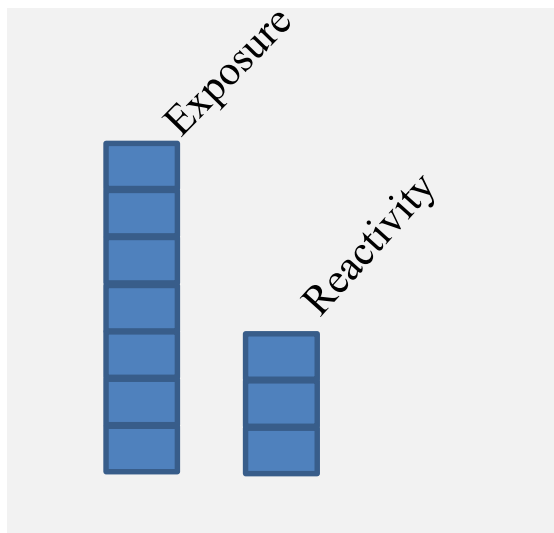
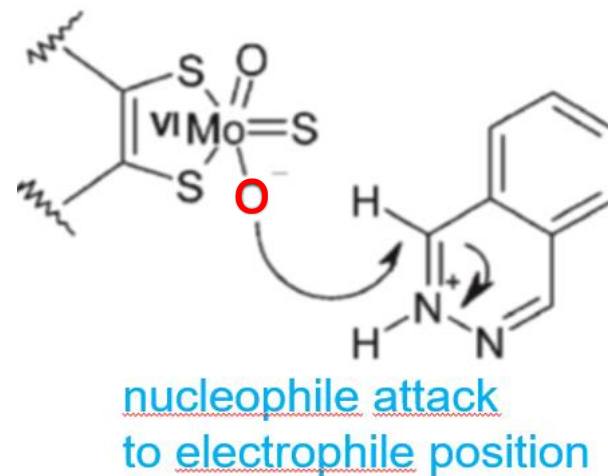


HEME  
radical

## FMO<sub>x</sub>

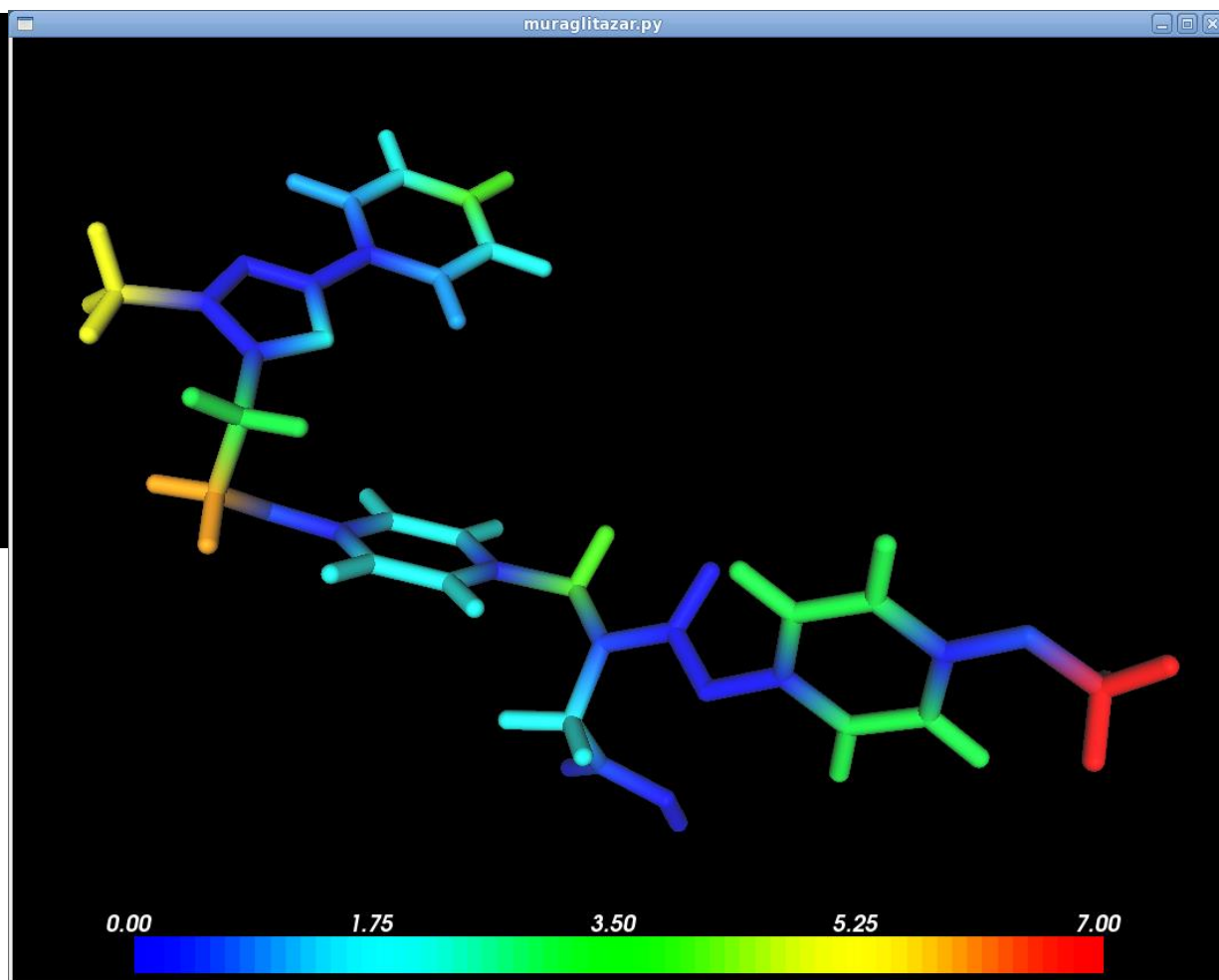
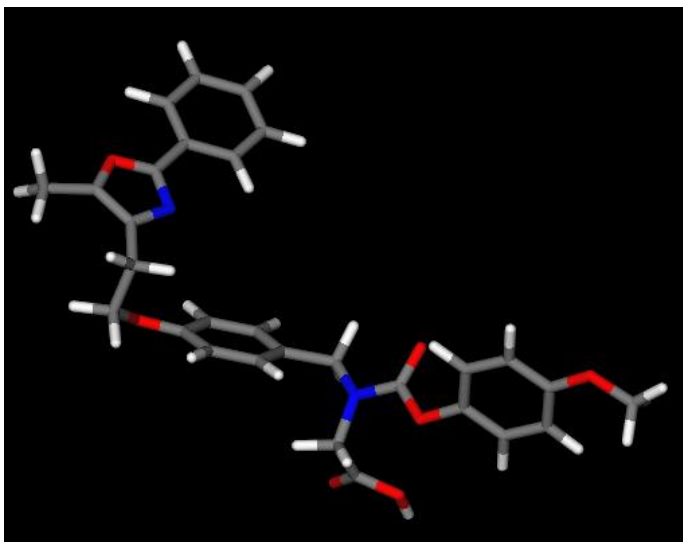


## AOX

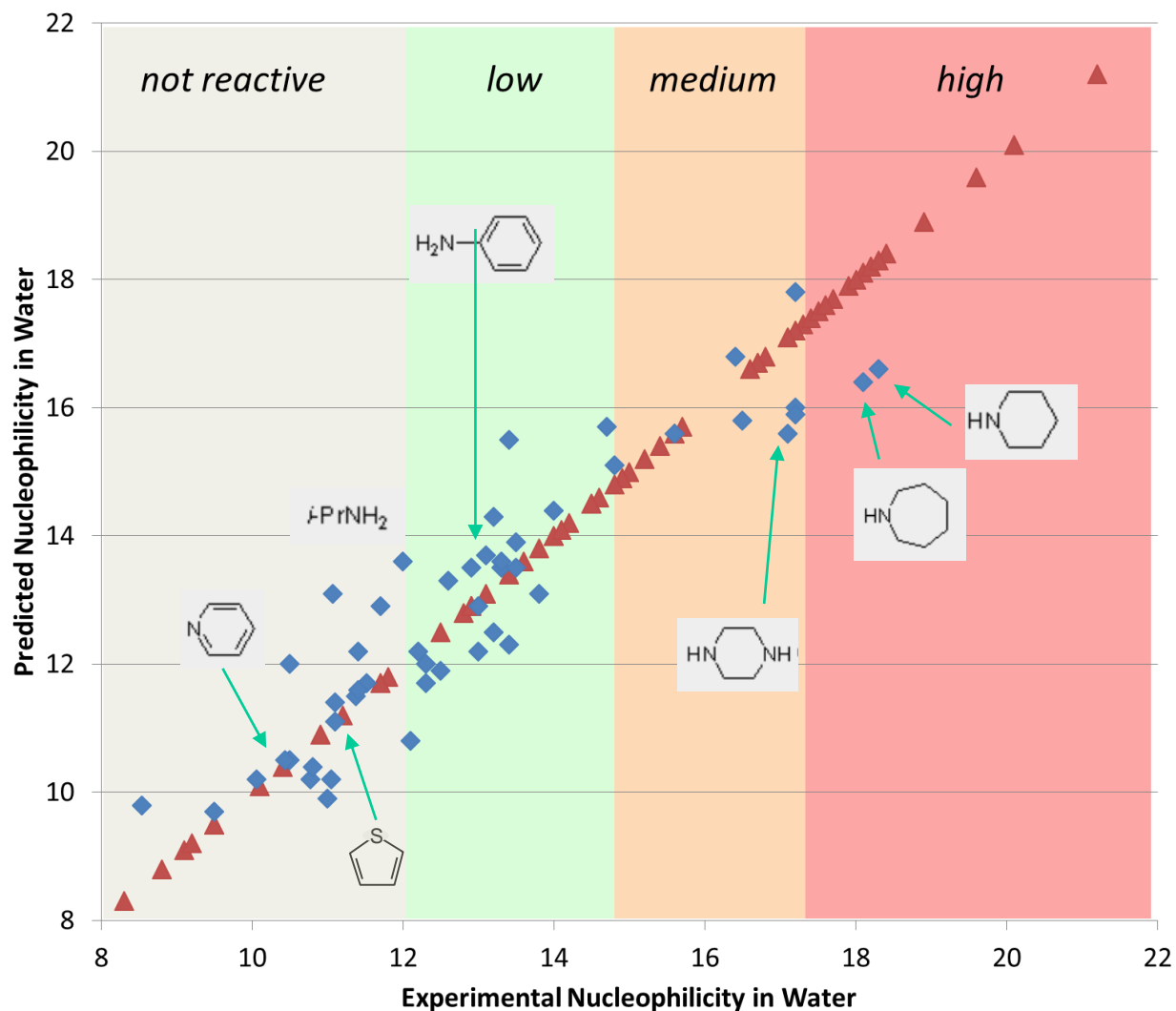


*CYPs reactivity module*

$$P_{\text{SoM},i} = (1 + w_e)E_i \underbrace{(1 + w_r)R_i}_{\text{red bracket}}$$



# prediction for 150 new fragments



$$P_{\text{SoM},i} = (1 + w_e)E_i(1 + w_r)R_i$$

# Porting to android and iOS



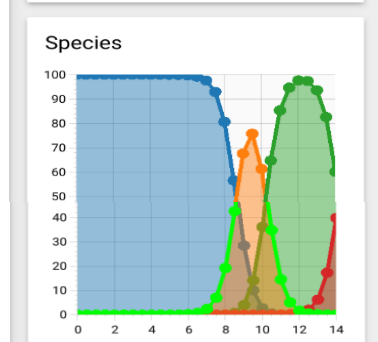
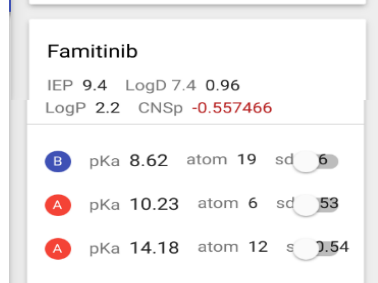
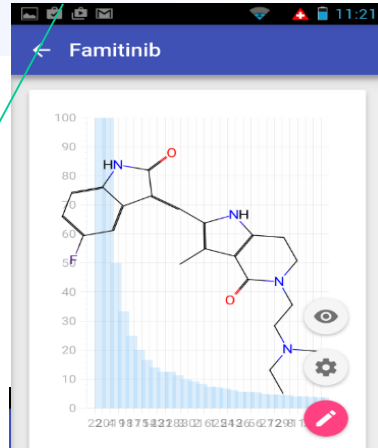
Chemodrome



android



Menu	Molecules	+
	Alprenolol	
	Famitinib	
	Thioridazine	
	Verapamil	
	Reboxetine	
	Noscapine	
	Estrone	
	N-desmethyl diltiazem	
	Rabeprazole	
	Cilostazol	
	Quinine	



client-server application:  
Calculations are performed on  
a cloud or remote server

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Thanks