Risks & benefits of the use of computational methods

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&

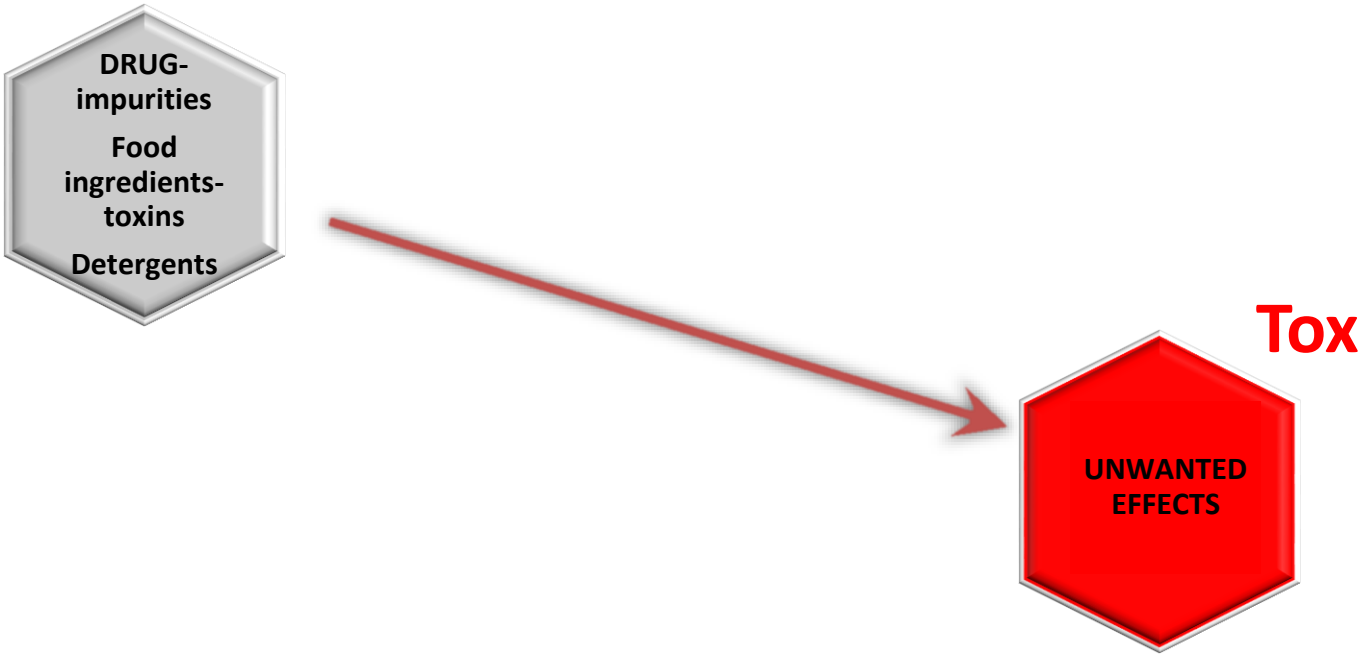
Molecular Discovery, London

Photos from Perugia, Umbria, Italy

Outline

1. Approaches for structure-property relationships
2. Limits of QSAR (QSPR) methods
3. Phenotype descriptors using –*omics* approach
4. Examples

1st approach: Structure-Property Relationships

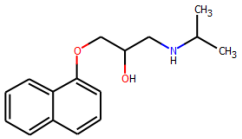


Risk-benefit assessment of medicinal products (A. Kouroumalis)

1st approach: Structure-Property Relationships

Chemical description
01100011100010101

xenobiotics



DRUG-impurities

Food ingredients-toxins

Detergents

Tox

UNWANTED EFFECTS

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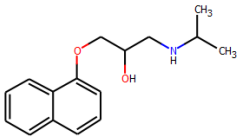

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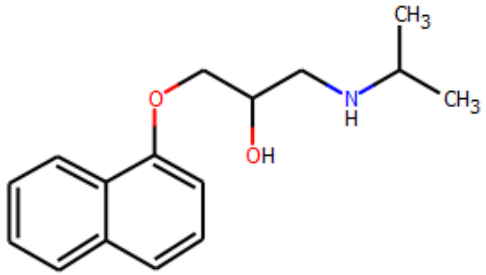

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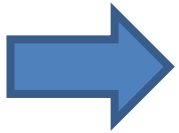

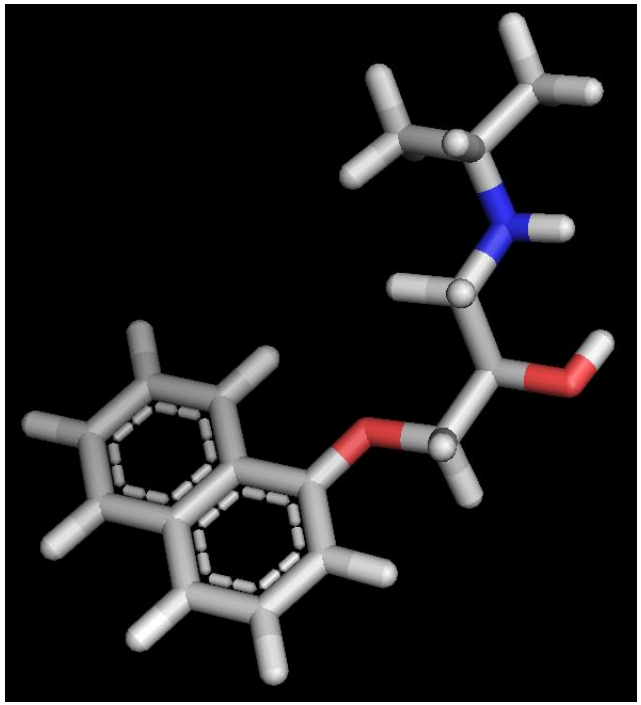

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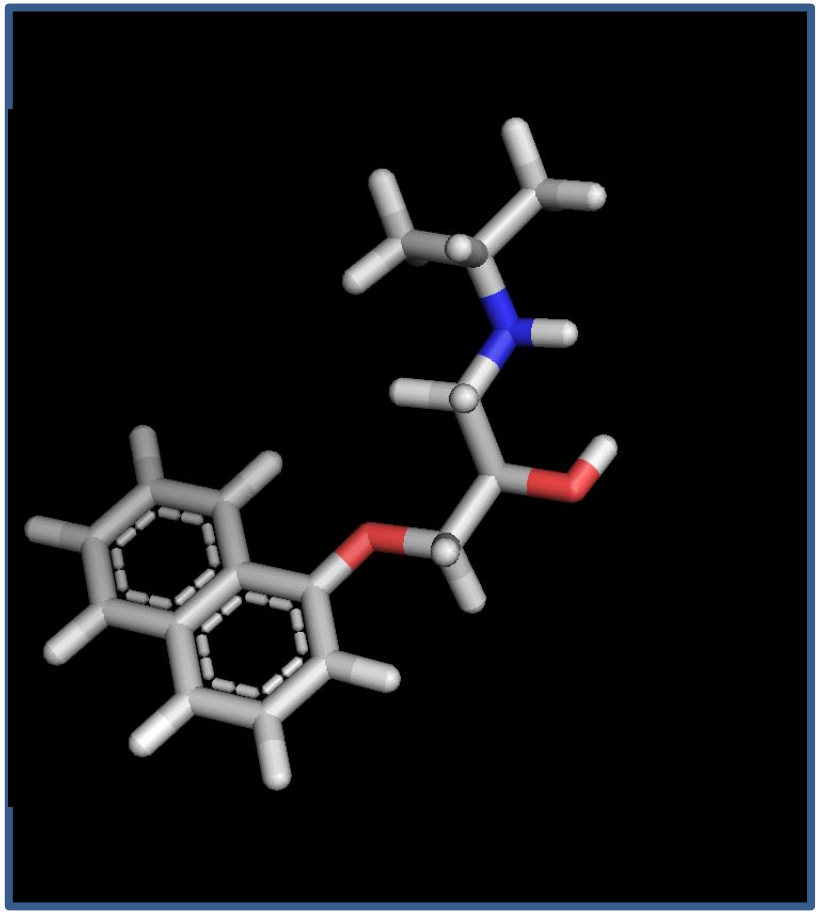

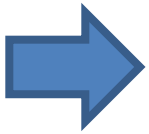

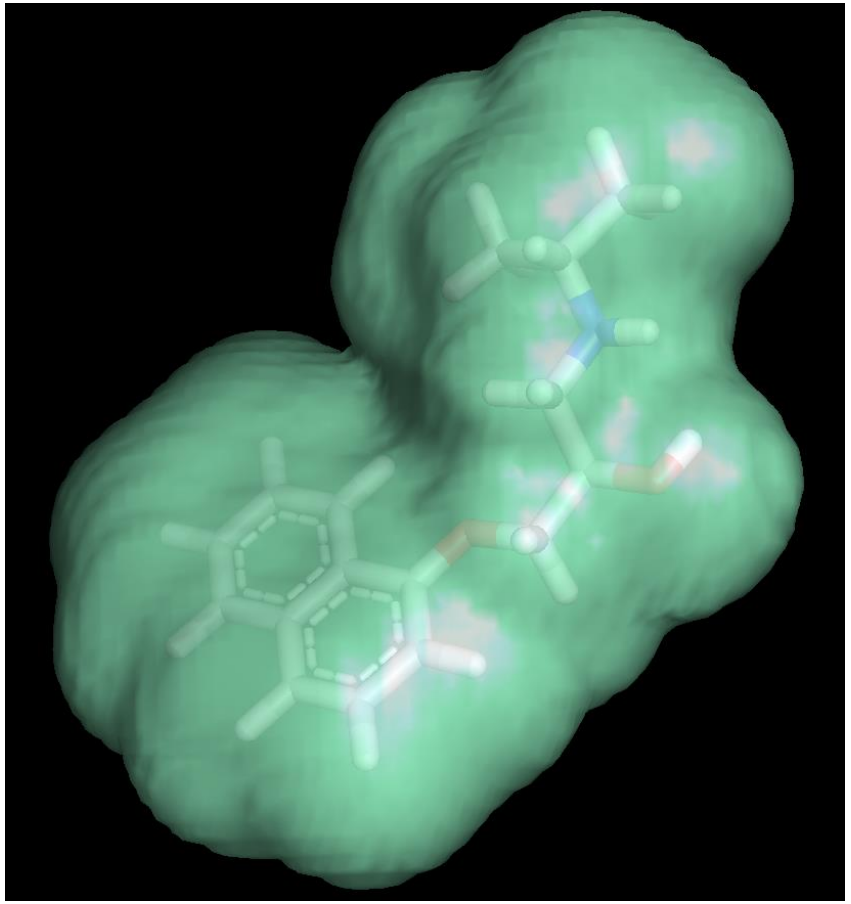

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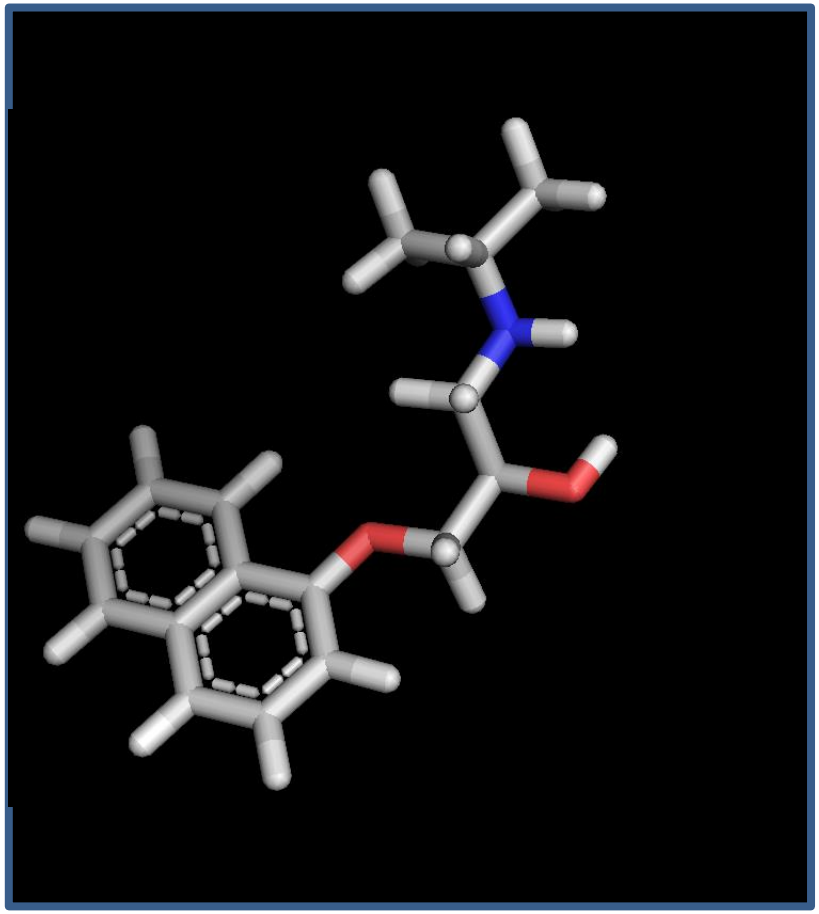

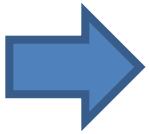

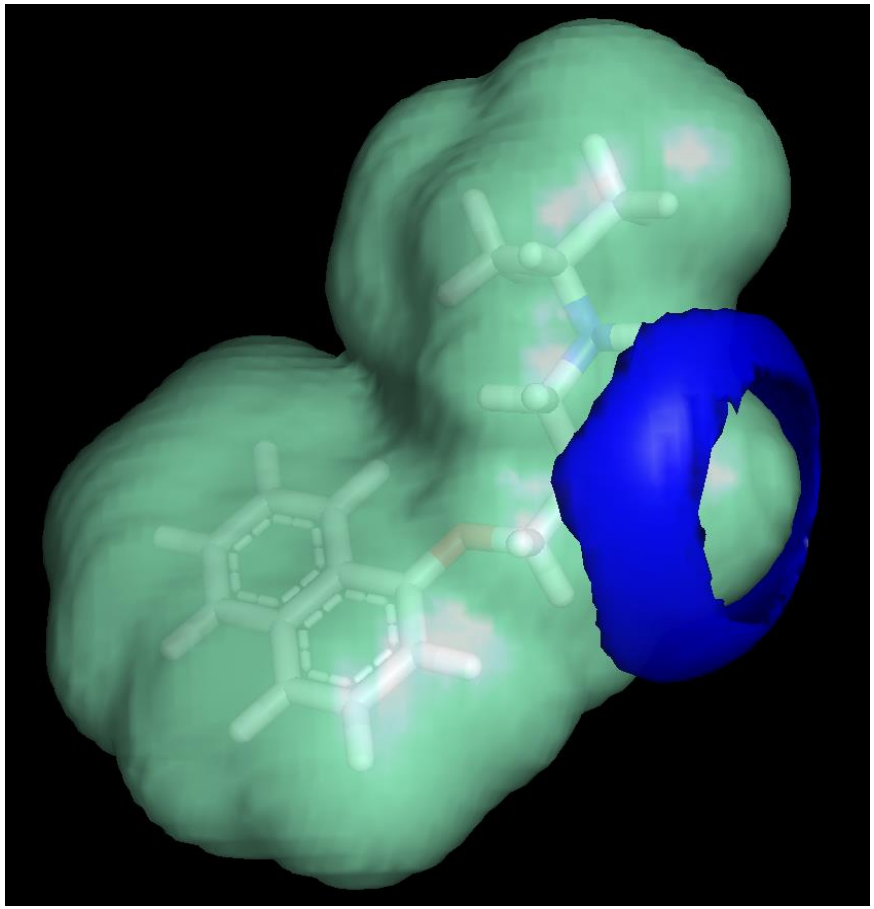

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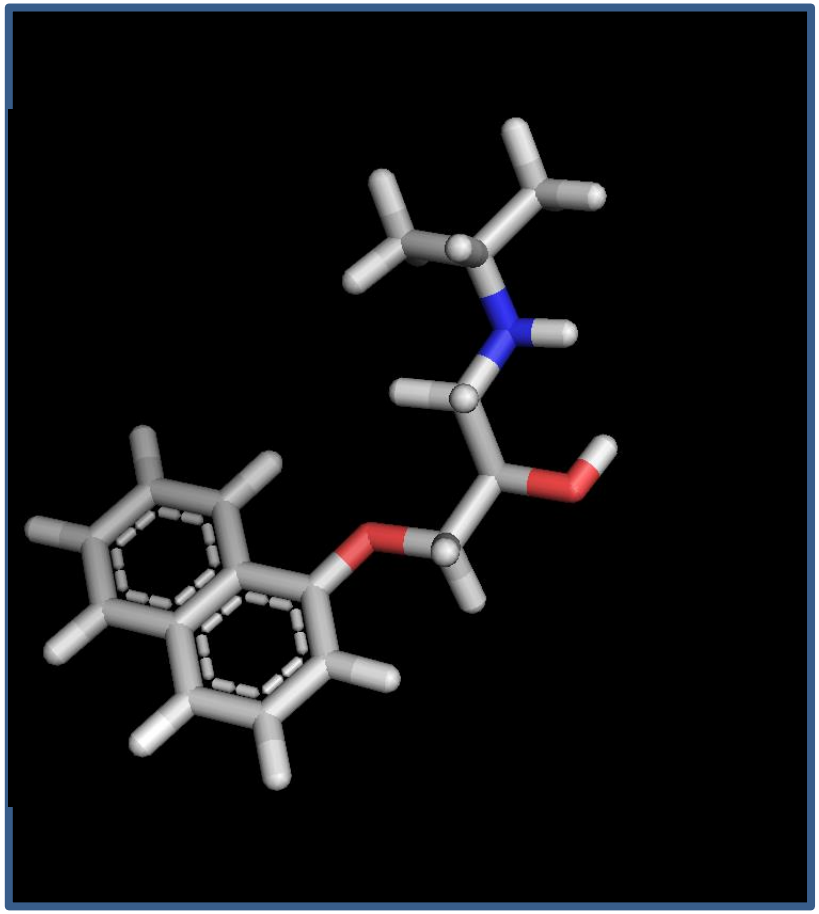
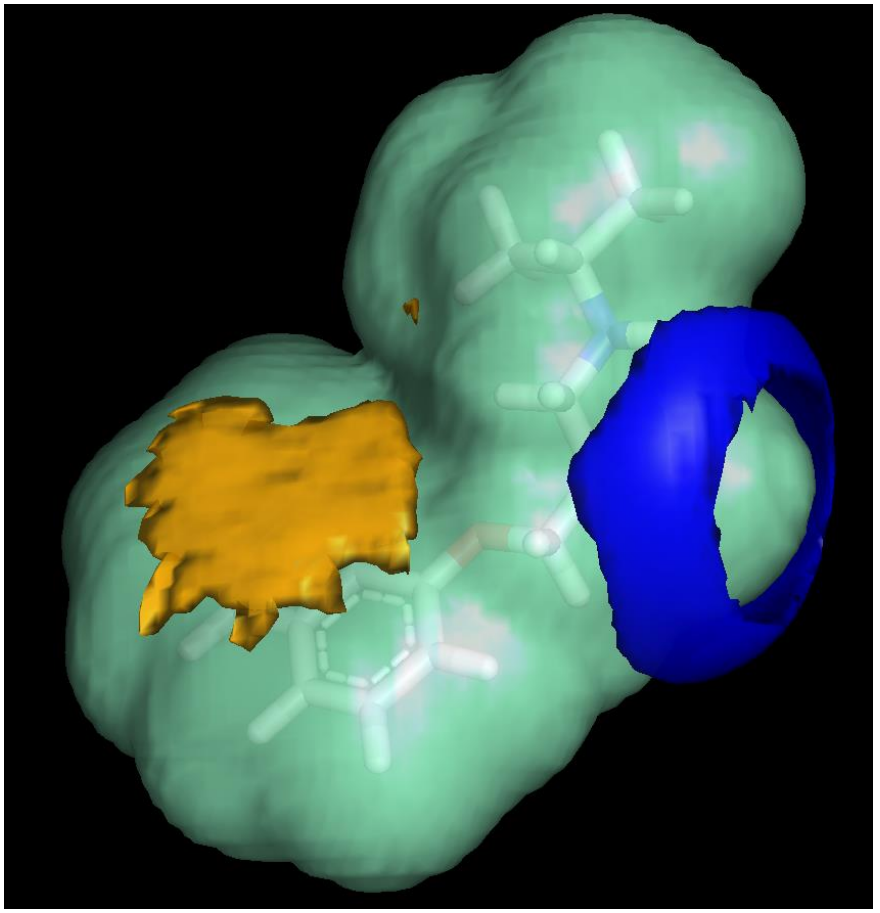
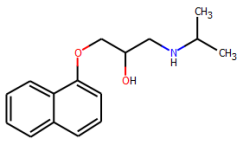
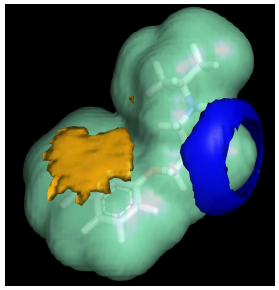




1st approach: Structure-Property Relationships

xenobiotics





Chemical description
01100011100010101

DRUG-impurities

Food ingredients-toxins

Detergents

AI

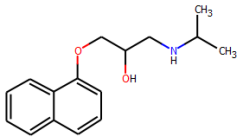
QSPR

Tox

UNWANTED EFFECTS

2nd approach: Structure-Property Relationships

xenobiotics

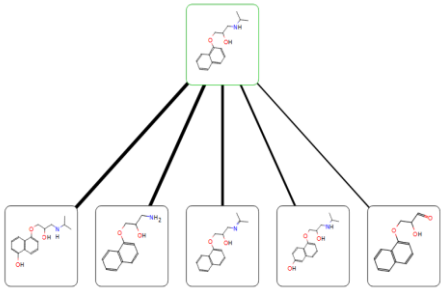


DRUG-impurities

Food ingredients-toxins

Detergents

Phase I metabolites
Phase II metabolites
Kinetics



METABOLITES

Chemical descriptions
01100011100010101

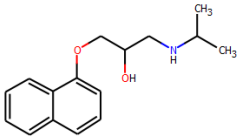
Tox

UNWANTED EFFECTS

hitroxen

3rd approach: Structure-Property Relationships

xenobiotics

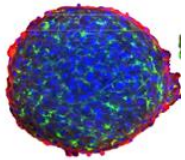


DRUG-impurities

Food ingredients-toxins

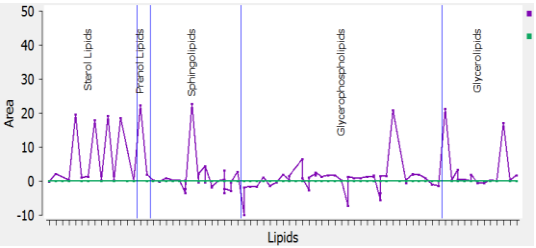
Detergents

organoids



METABOLITES

Phase I metabolites
Phase II metabolites
Kinetics



METABOLOMICS
LIPIDOMICS

phenotype description
01100011100010101

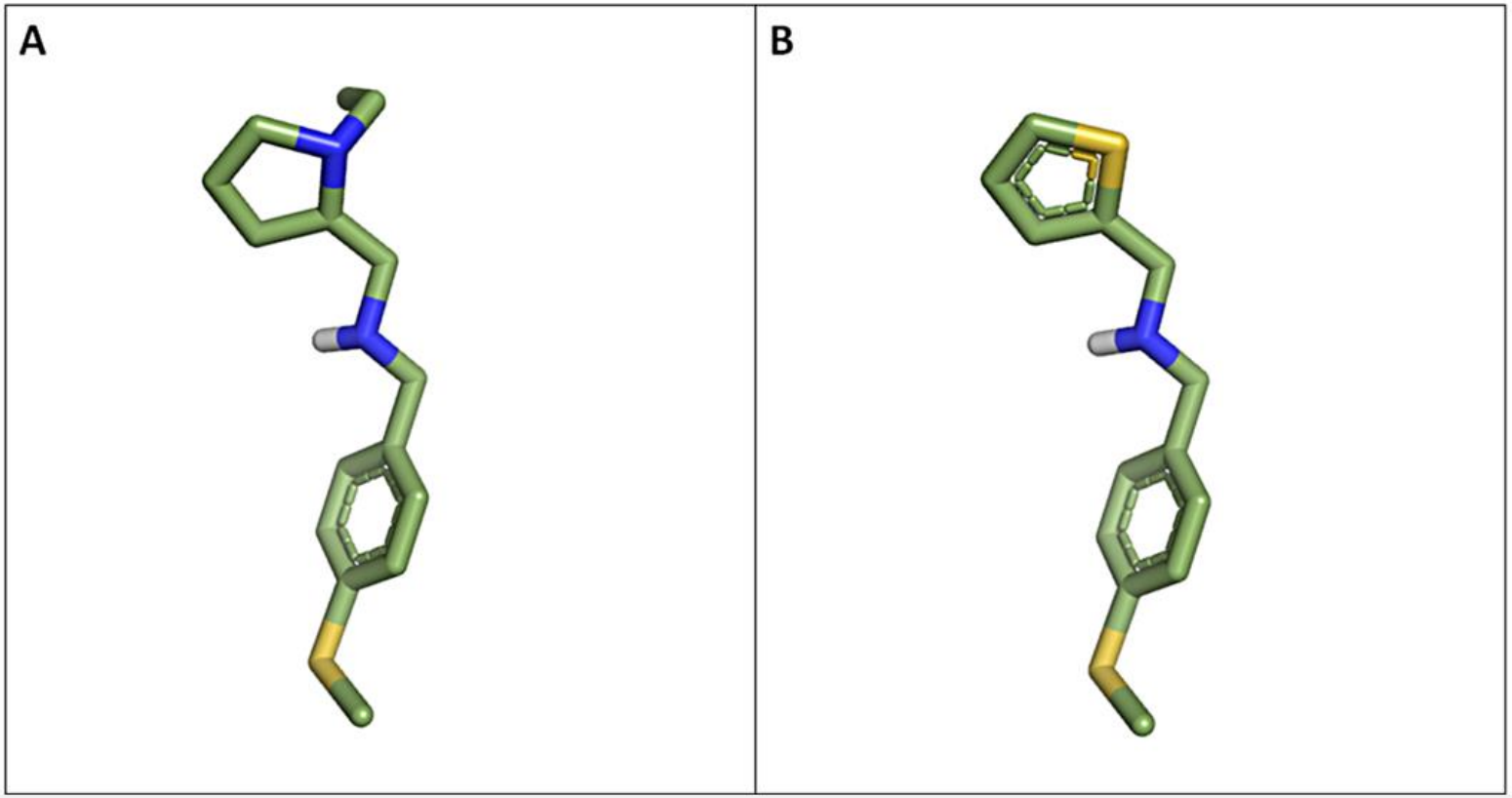
UNWANTED EFFECTS

Tox

example

noTox

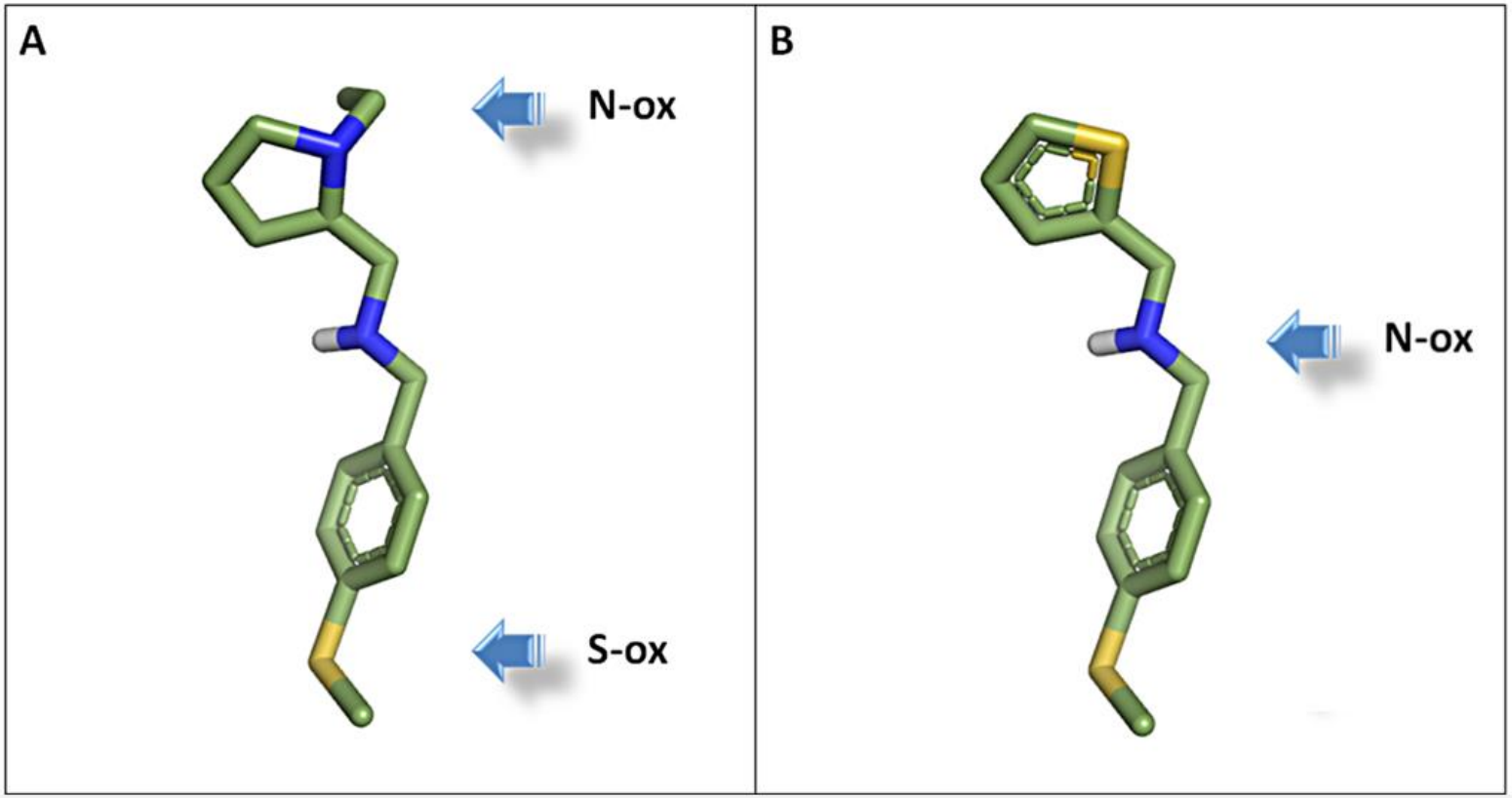
Tox



example

noTox

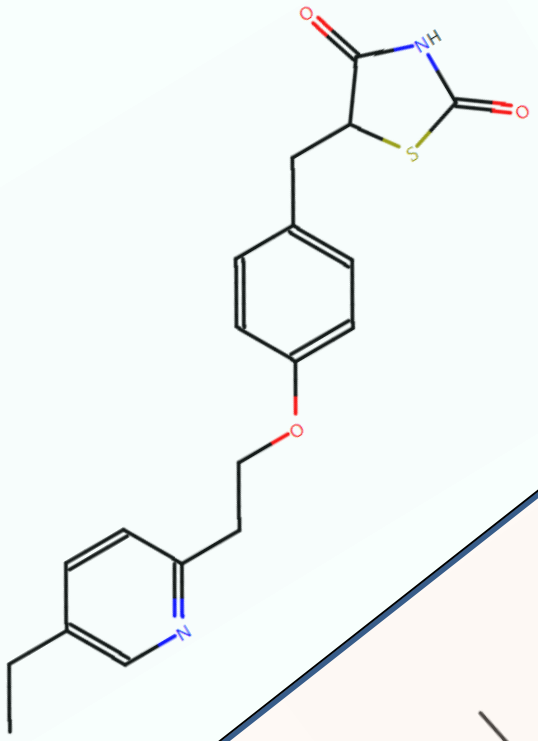
Tox



Thiazolidinediones tox pathway: Oxidative CYP3A4

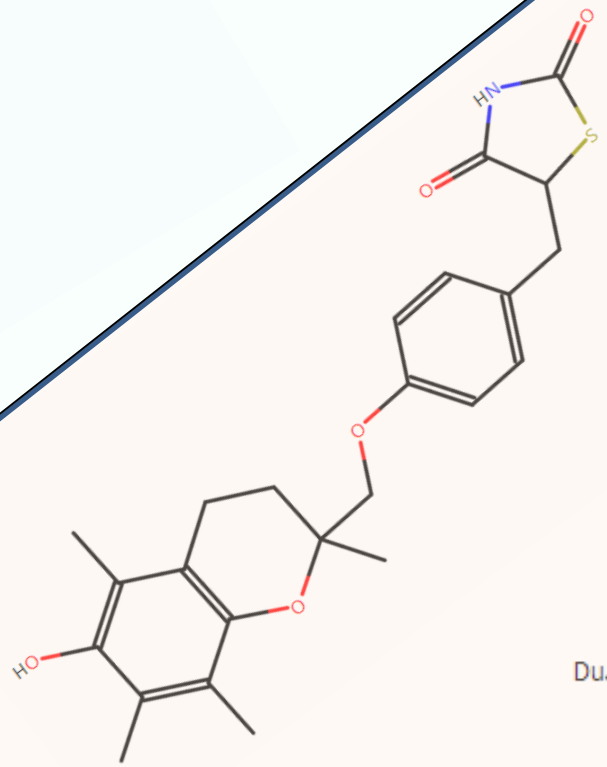
Kassahun et. al. Chem. Res. Toxicol. (14), 62-70, 2001

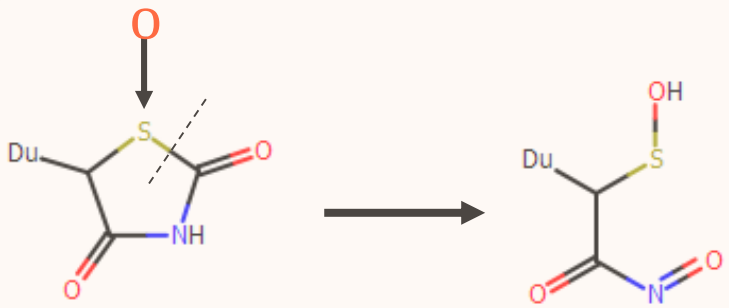
Pioglitazone



Troglitazone

Hepatotoxic





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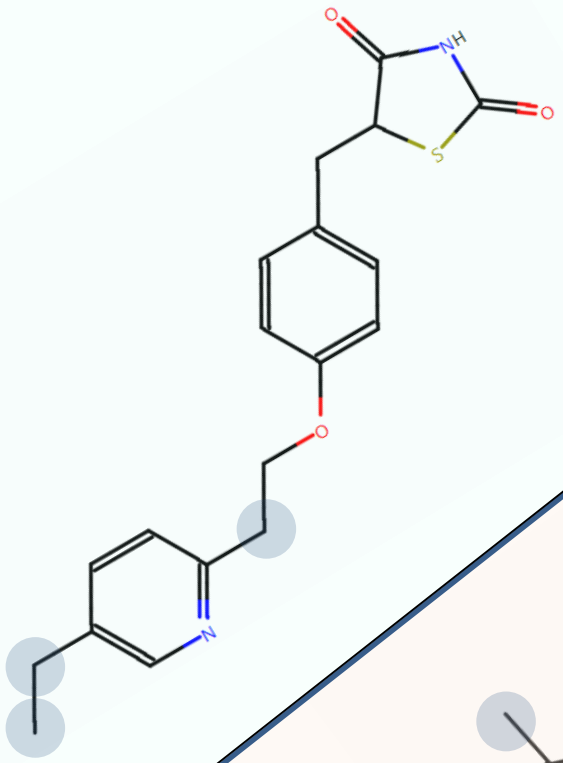

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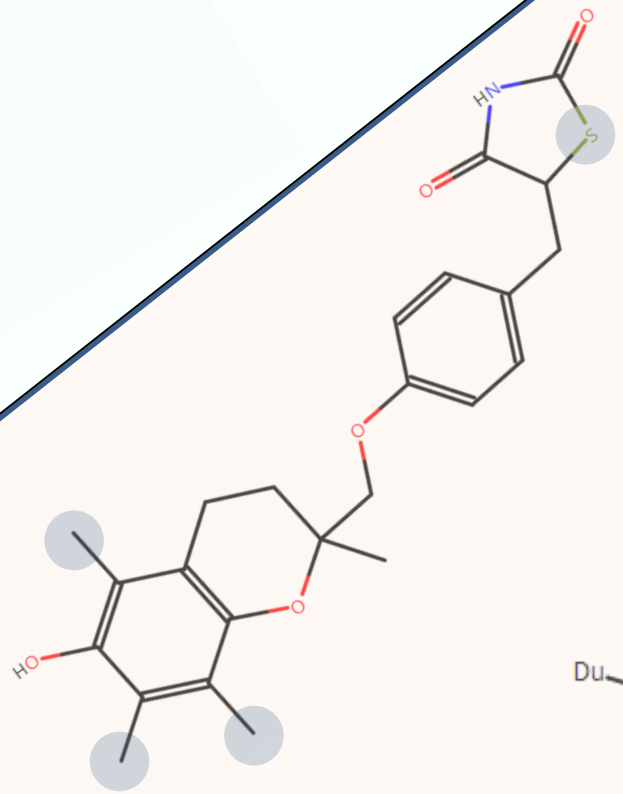
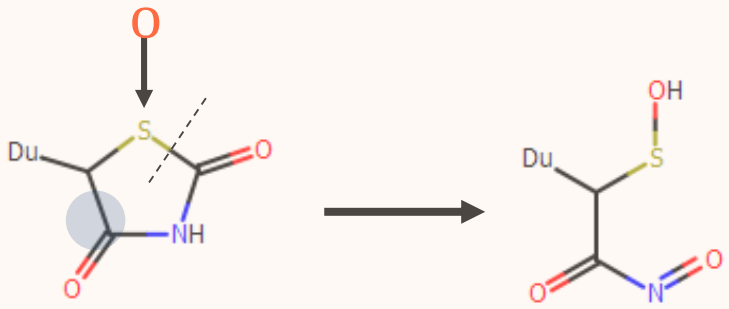
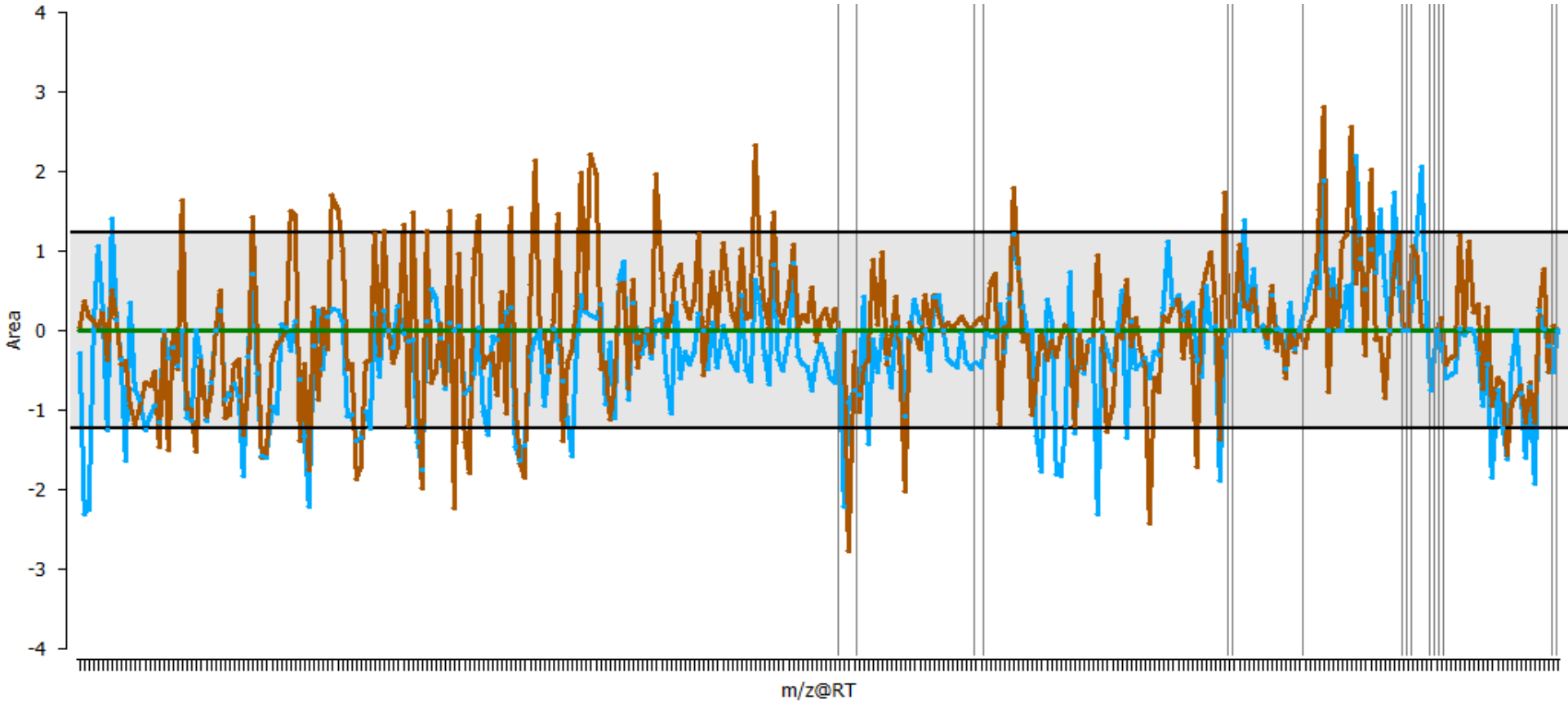




Pioglitazone

Troglitazone

12 days human MIT hepatocye



Pioglitazone
Troglitazone
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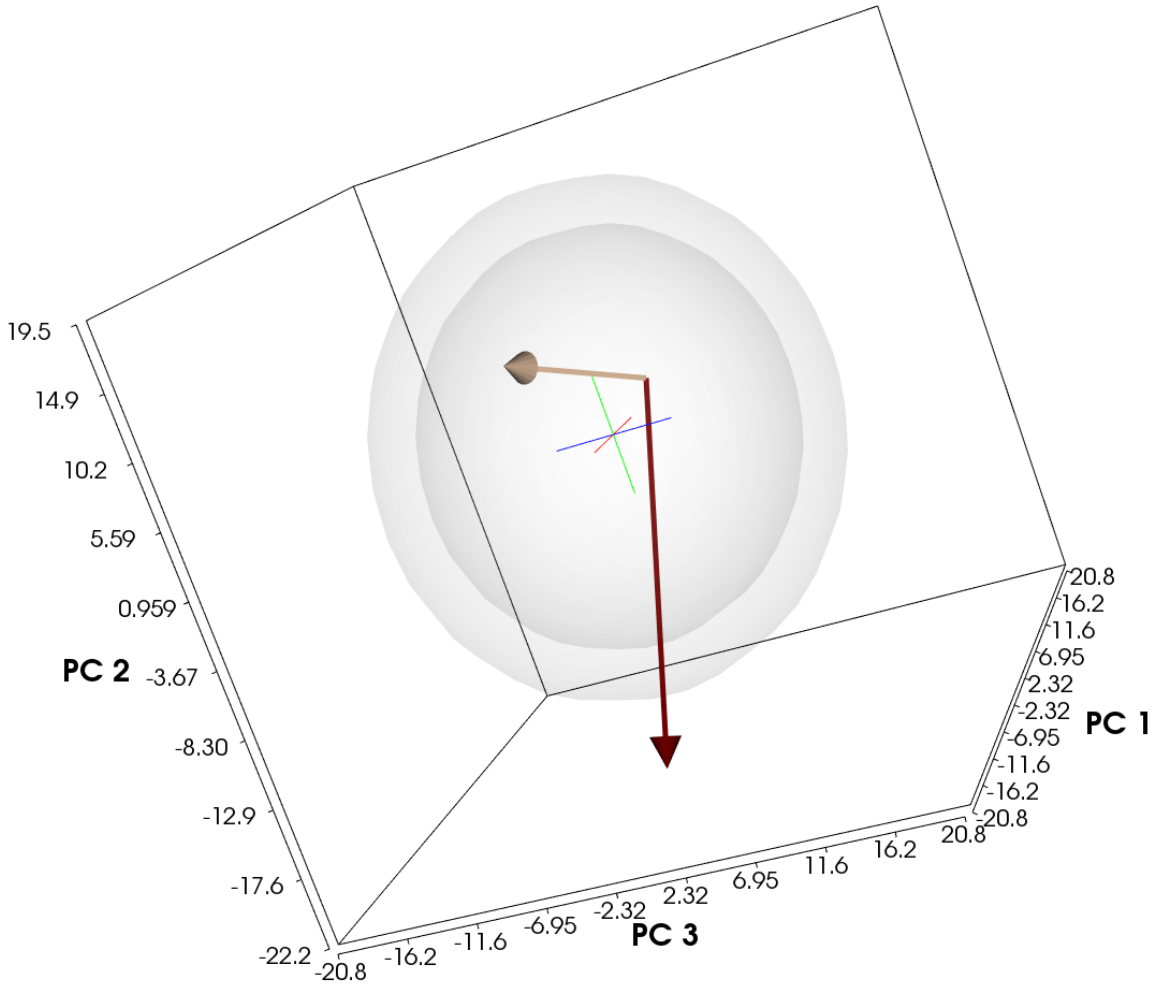
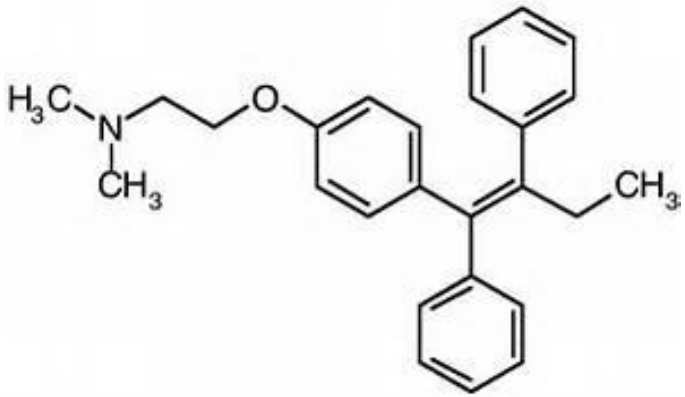


Benefit: prevent breast cancer

Risk: increased risk of uterine cancer, stroke

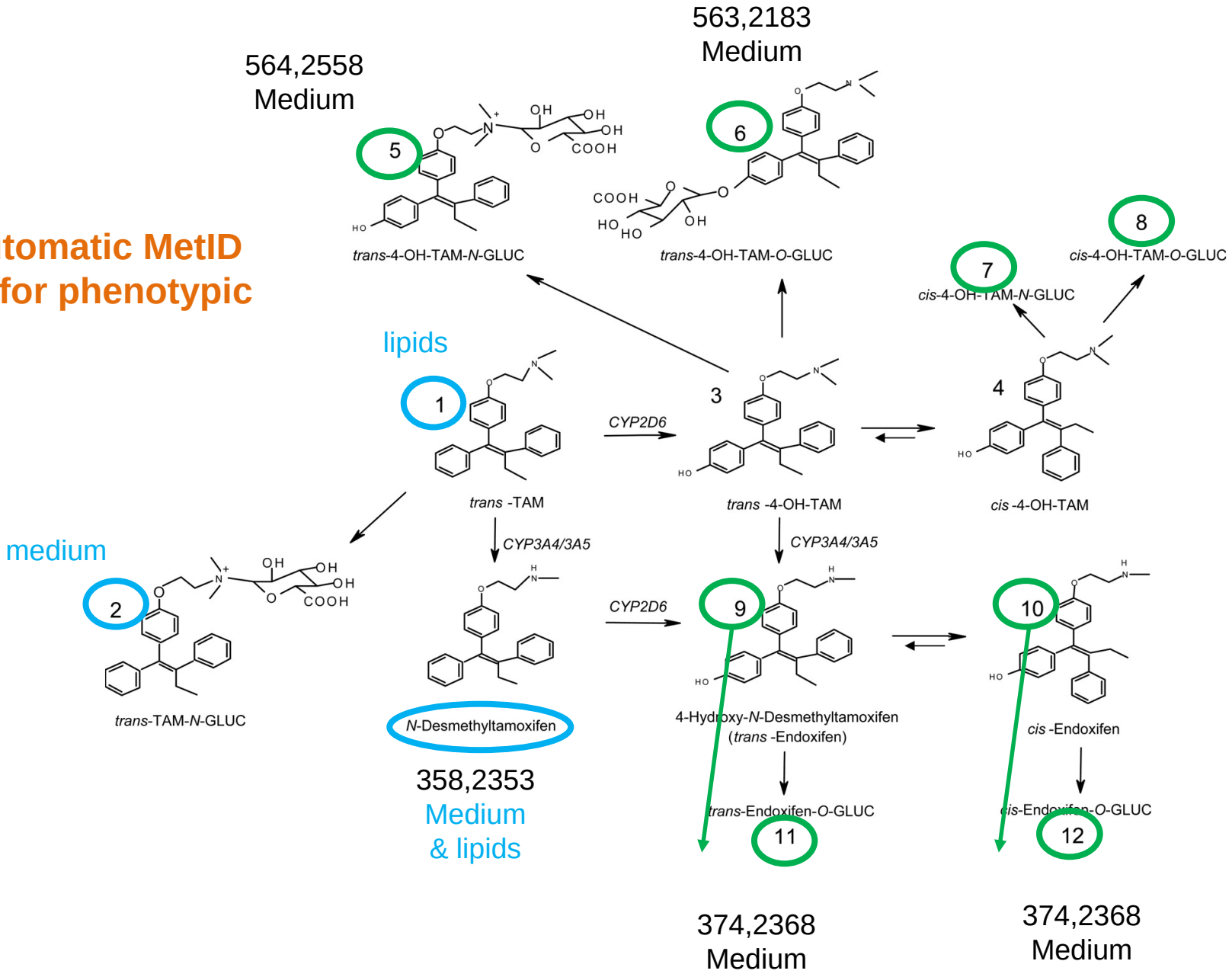
Risk / Benefit ??



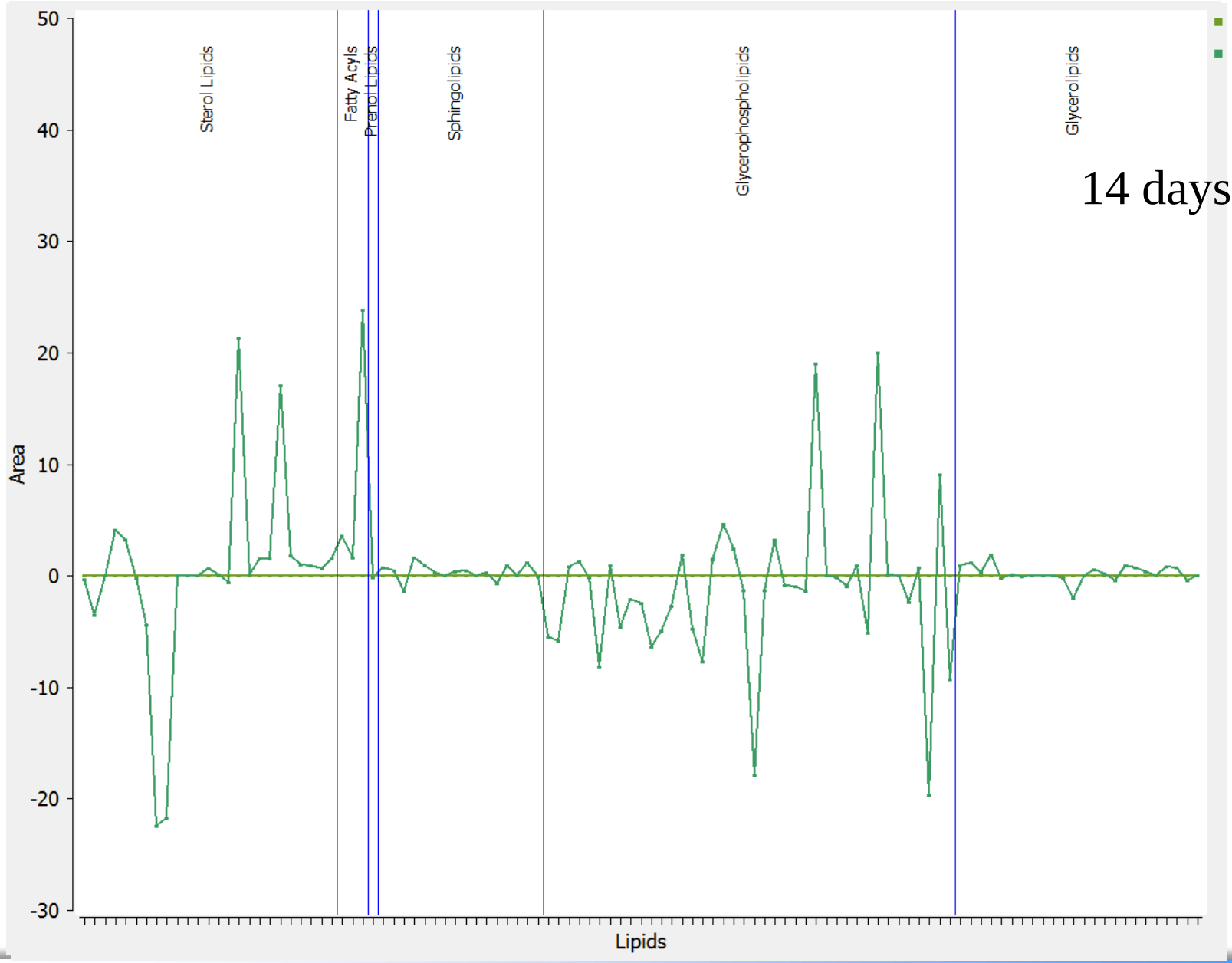
Tamoxifen DILI+
(Steatohepatitis)

Personalised approach

Ultra fast automatic MetID & lipidomic for phenotypic fingerprint



LipoTox Technology Platform



ctrl e TAM

Scores

Objects

Projections

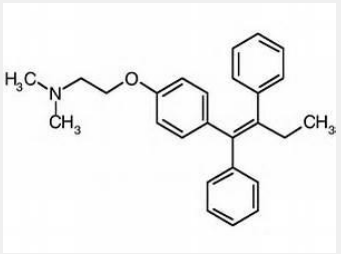
Back Projection

Style

Label Style

Generate boundaries

Clear boundaries



Tamoxifen DILI+
(Steatohepatitis)

Toxicity increases

PC2

PC1

CTRLveh

TAM 10

TAM 30

What Can We Do With LipoTox Profile Data?

- **Analyze overall toxicity profiles**
  - Profile characteristics
  - Unsupervised and supervised approaches to compare profiles
- **Focus on individual endpoints**
  - Correlate to external data
  - Build an understanding of clinical mechanisms

Applications

- **Compound characterization**
  - ADME Property profiles
  - Pathways, possible clinical indications
- **Mechanism of action**
  - Unexpected off-targets (toxicity)
- **Support therapeutic hypotheses**
  - Compare to competitor molecules, clinical standards of care
  - Identify translational biomarkers

Drug Combinations

- **Challenges for studying drug combinations:**
  - System may include more drugs
  - Suitably robust to capture combination effects

MALDI (DESI) Metab-Lipid-omics (looking for locations in space)

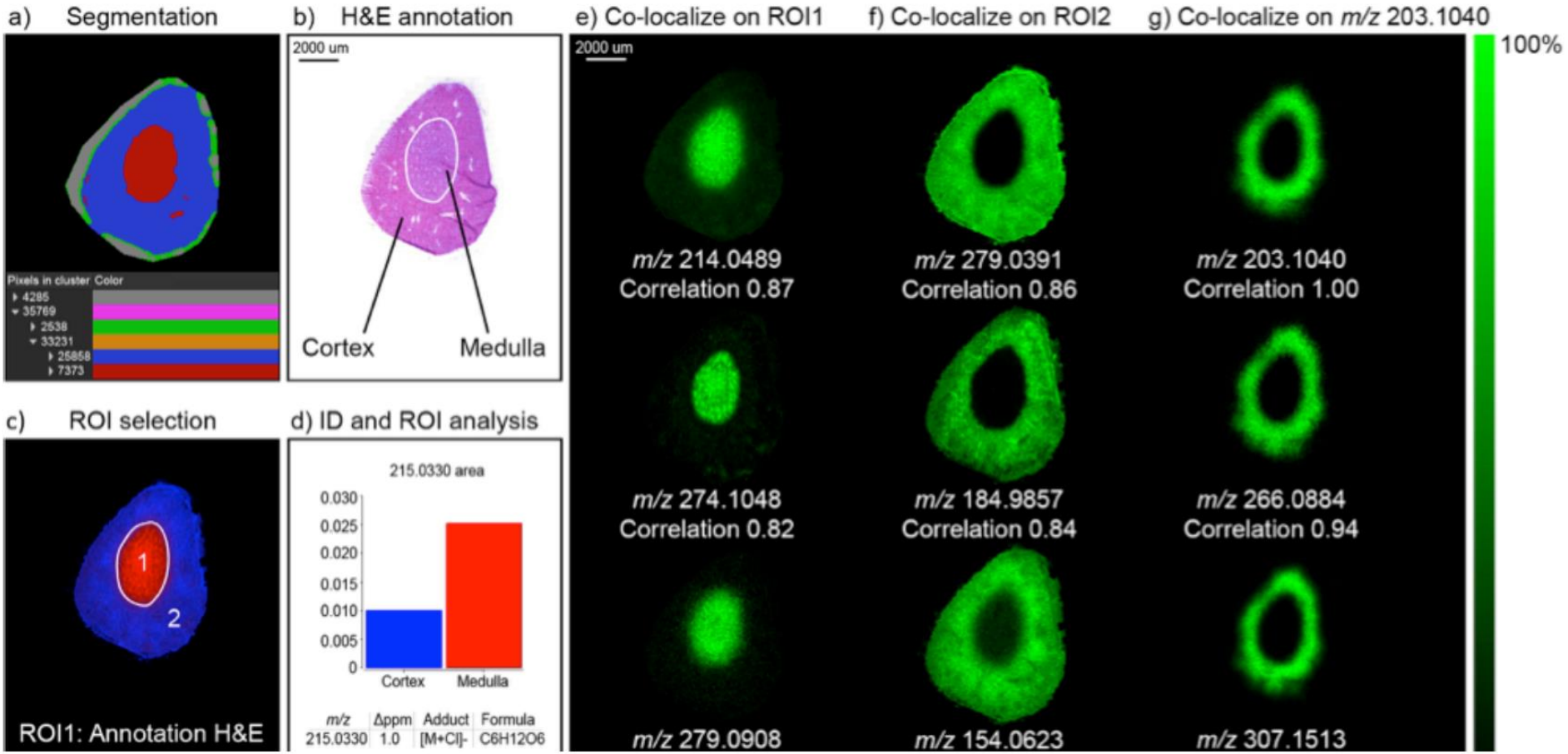


Figure 2. Example data analysis pipeline for metabolite MSI of rat kidney tissue. (a) Bisecting k-means segmentation is performed and enables differentiation of medulla (red) and cortex (blue). (b) Optical image of the analyzed tissue section following MSI acquisition and stained with H&E. The medulla region is annotated with a white circle. (c) Regions-of-interest (ROIs) are defined using both annotated regions from stained tissues (ROI1, red) and from bisecting k-means segmentation shown (ROI2, blue). From the regions a variety of univariate and multivariate analyses can be performed for both inter- and intra-sample comparisons. (d) The peak area for an ion at *m/z* 215.0330 within ROI1 and ROI2. This ion is automatically identified as the $[M+Cl]^-$ ion of an analyte with molecular formula $C_6H_{12}O_6$, most likely a sugar. Finally, automatic identification of ion signals that co-localize with ROI's (e, f) and *m/z* values (g) is performed. The scale bar on the right indicates relative intensity.

Thanks to …

Alessandra Di Veroli
Aurora Valeri
Fabien Fontain
Laura Goracci
Massimo Baroni
Paolo Benedetti
Paolo Tiberi
Sara Tortorella
Stefano di Bona

Molecular Discovery


Rosso di sera .. bel tempo si spera !!
Red sky at night, shepherd's delight
Thanks all …