

Infrared Ion Spectroscopy

Small-molecule identification in MS analysis

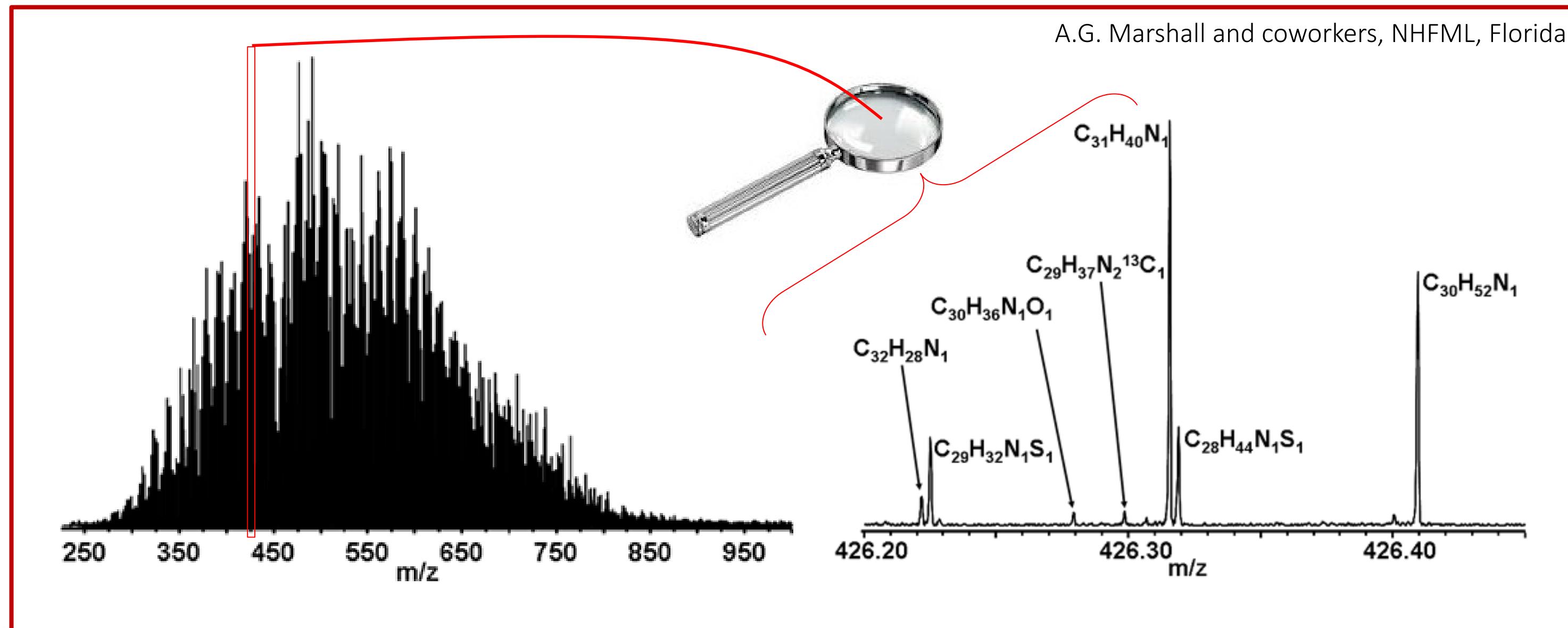
Jos Oomens



Mass spectrometry as analytical method: a quick SWOT analysis

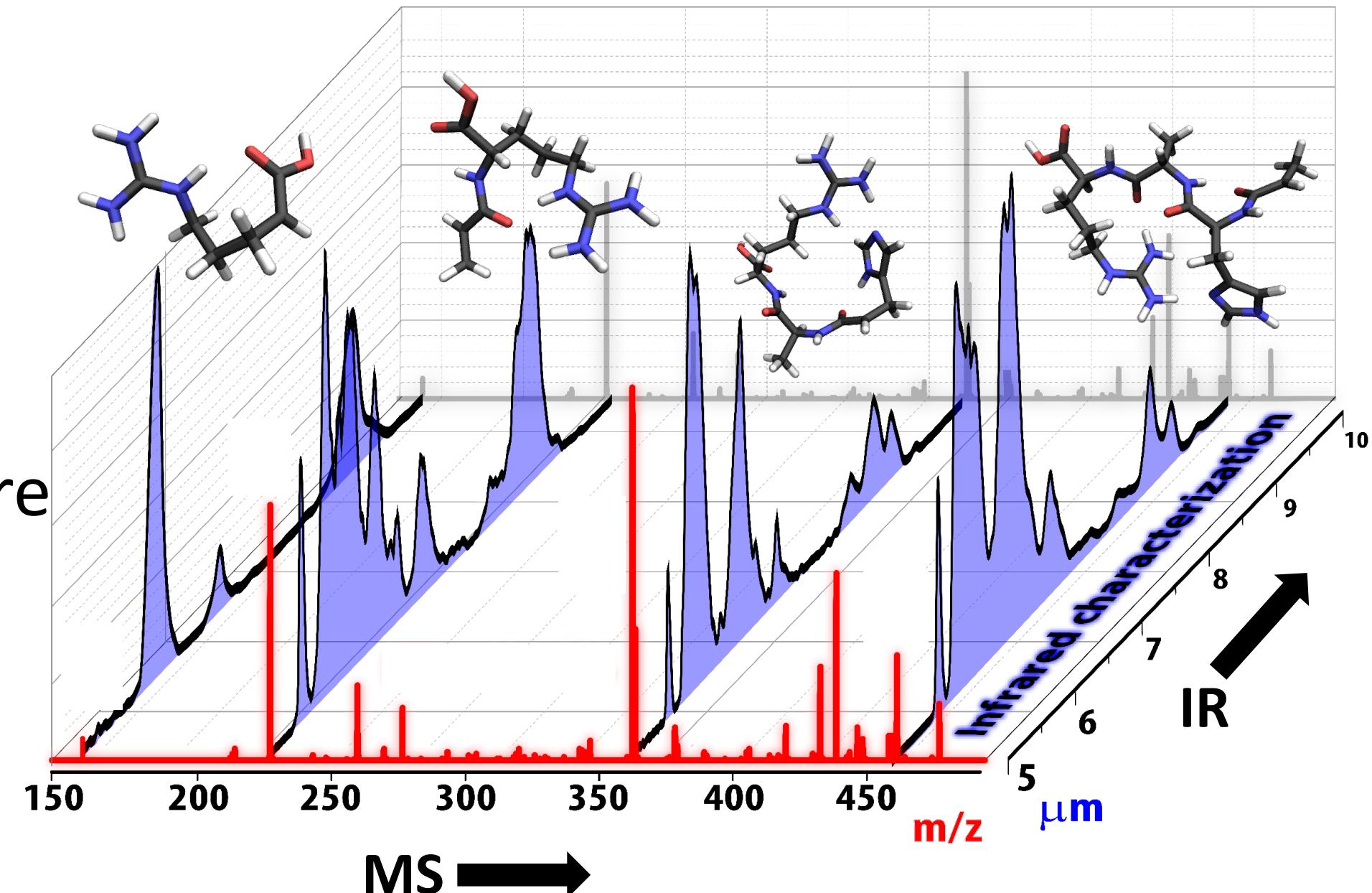
- 😊 high sensitivity
- 😊 high resolution
- 😊 high peak capacity

😢 limited molecular structure info



Spectroscopic methods – quick SWOT

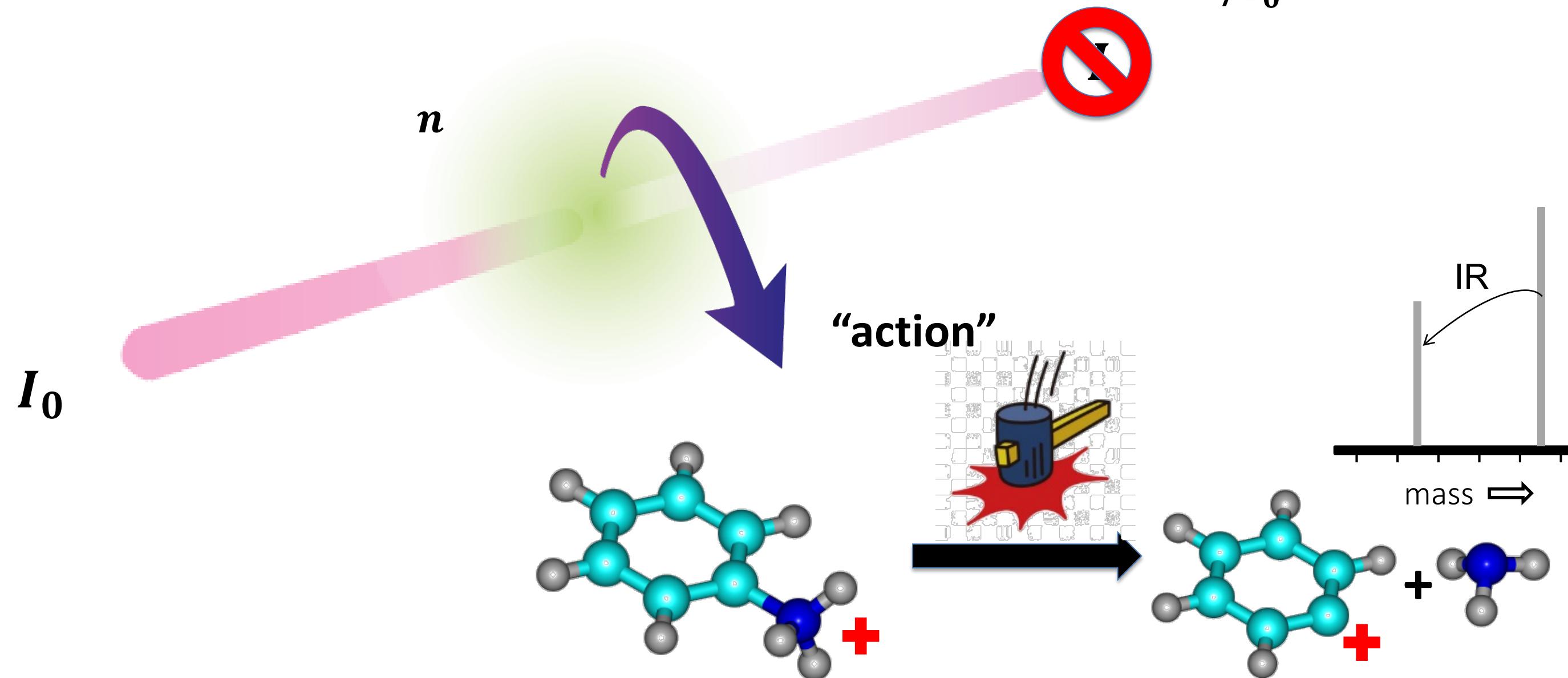
- 😊 Structurally diagnostic
- 😊 Spectra predictable by QC
- 😢 Poor separation in complex mixture analysis
- 😢 Sensitivity nowhere near MS



Integrate MS and IR → IRIS

Transmission versus Action spectroscopy

ion density in MS $<< 10^6 \text{ cm}^{-3}$
transmission: $I/I_0 = e^{-\sigma n L} \approx 1$

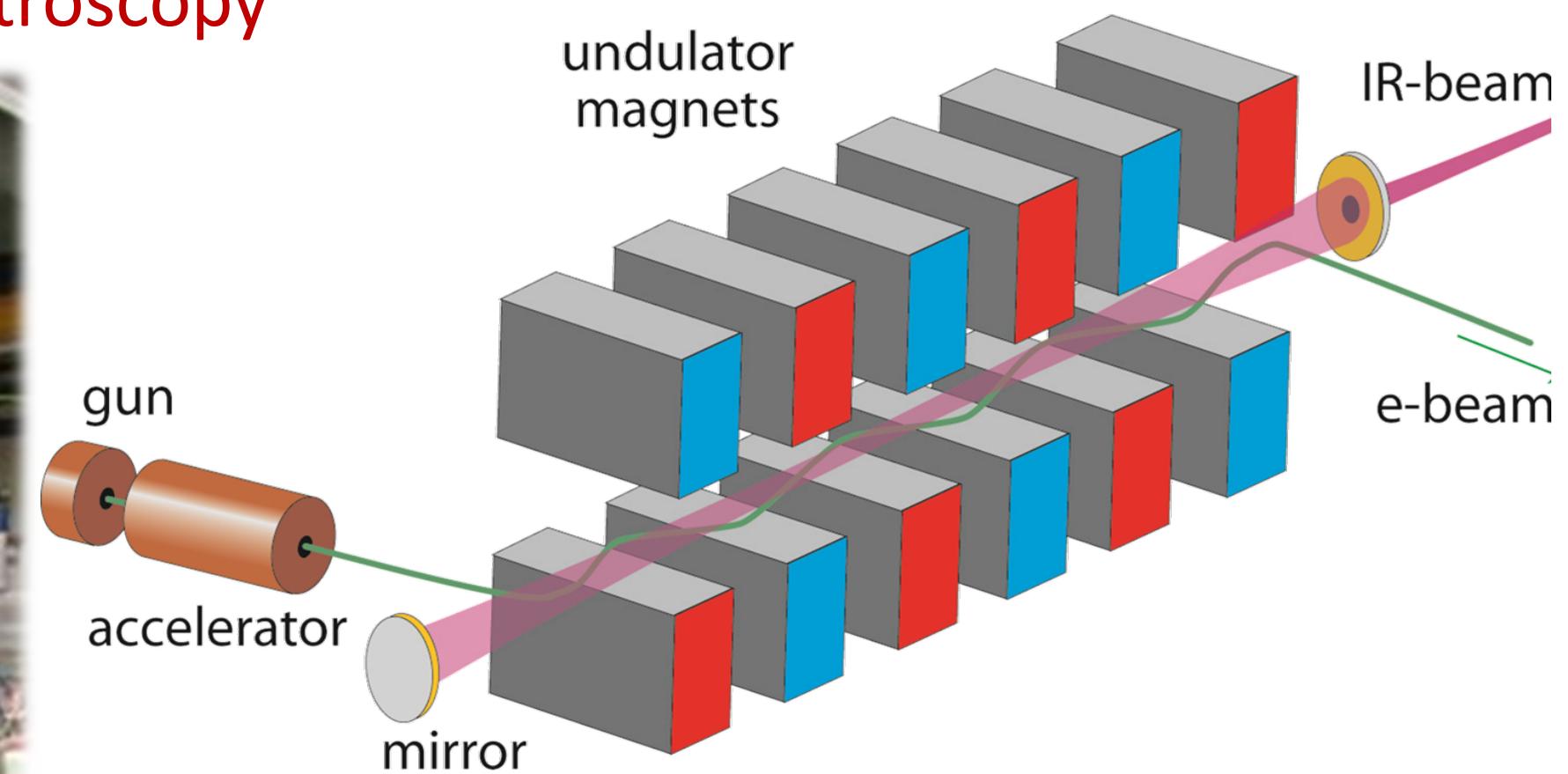


Infrared Ion Spectroscopy (IRIS)

Integration of mass spectrometry and IR spectroscopy



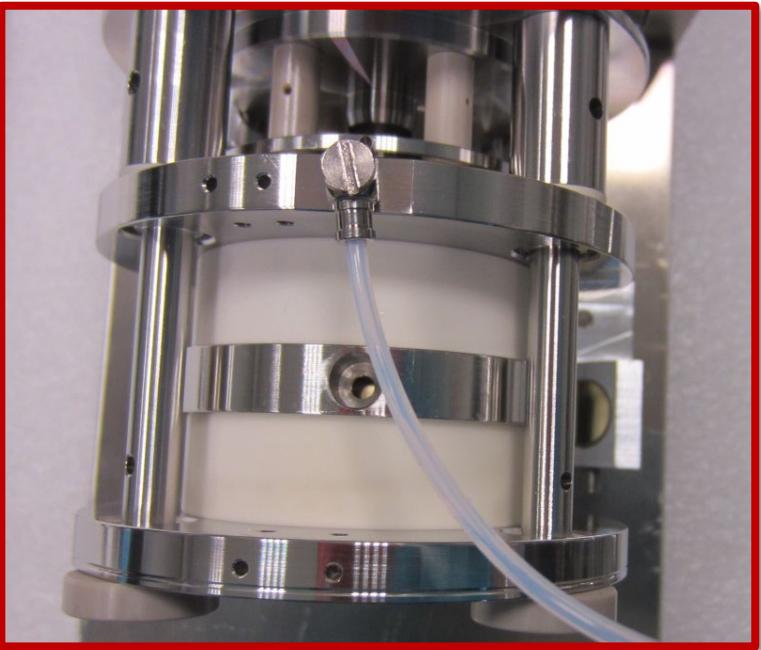
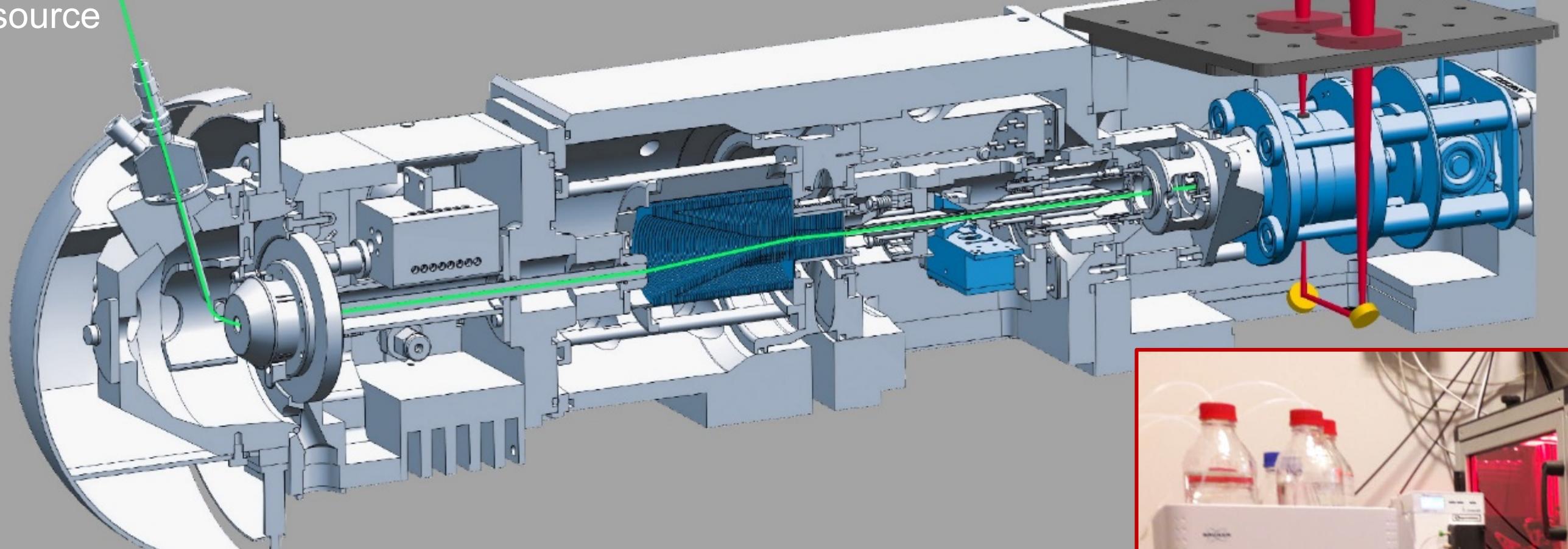
FELIX infrared free-electron laser
Broad wavelength coverage in IR



- User facility
- Wavelength tunable 3 – 150 μm
- Pulse energy <100 mJ per 5 ms pulse
- FWHM bandwidth >0.4% of λ

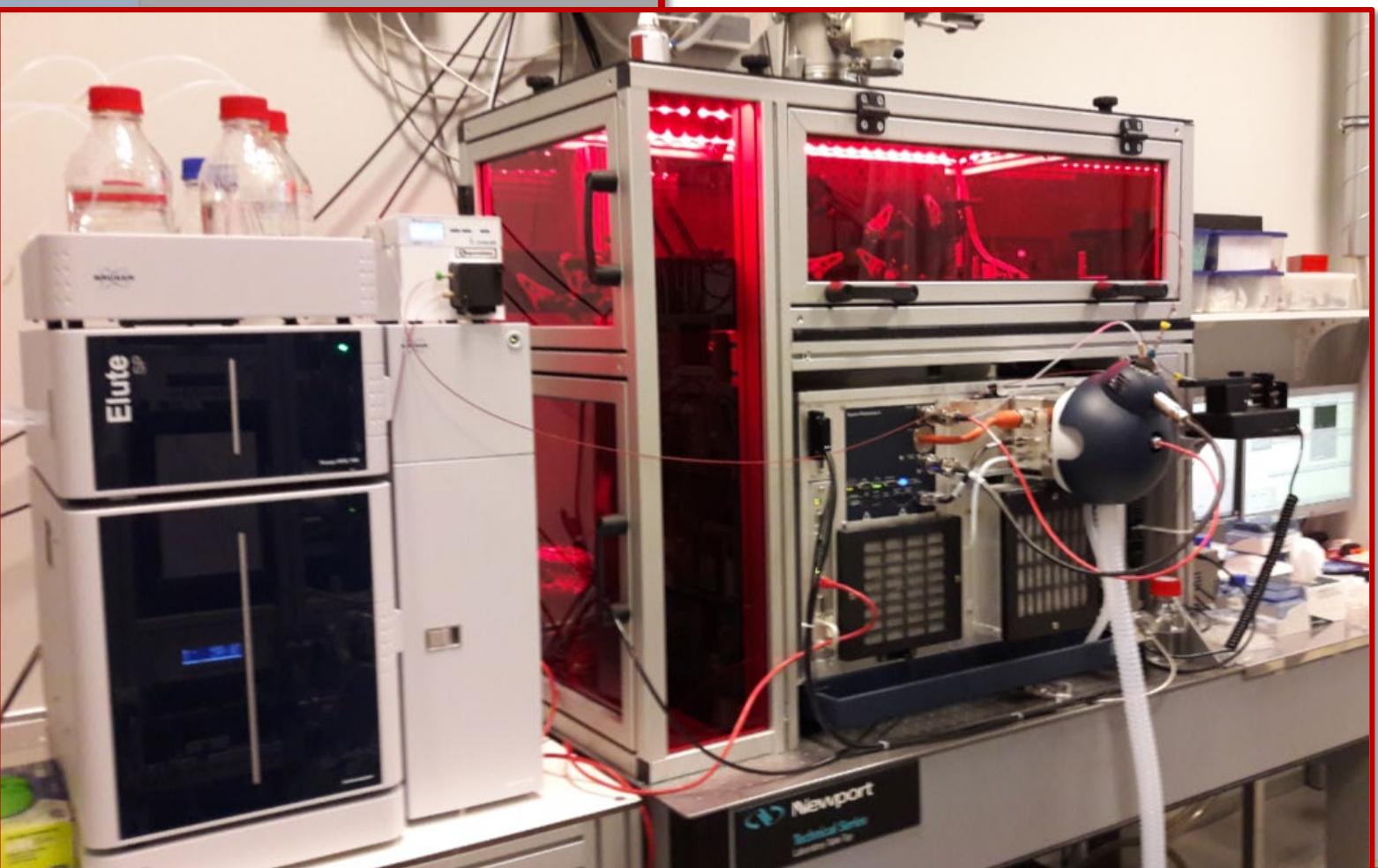
ESI ion source

FELIX IR beam



Mass Spectrometer Bruker Amazon Ion Trap MS

Martens, Berden, Gebhardt, Oomens, *Rev. Sci. Instrum.* **2016**, 87, 103108



Metabolic diseases

(inborn errors of metabolism, stofwisselingsziektes)



Newborn screening



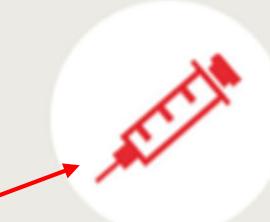
Doodsoorzaak

Metabole ziekten zijn één van de grootste doodsoorzaken onder kinderen in Nederland.



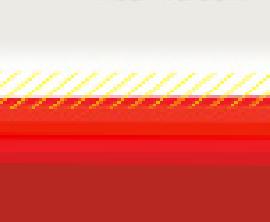
10.000

Er zijn in Nederland meer dan 10.000 gezinnen met één of meerdere kinderen met een metabole ziekte.



Hielprik

Er zijn ruim 1.000 metabole ziekten waarvan er nu 14 in de hielprik zitten. Dit moeten er veel meer worden.



Aftakeling

Voor veel kinderen is er nog geen behandeling. Zij raken verstandelijk en lichamelijk beperkt en overlijden vaak jong.



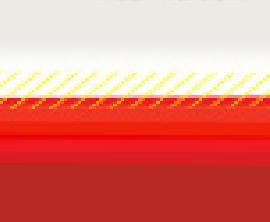
Erfelijk

Metabole ziekten zijn meestal erfelijk en ontstaan door een defect op een gen.



Hoop

Artsen verwachten dat binnen 30 jaar vrijwel alle metabole ziekten behandelbaar zijn, mits er voldoende geld is voor onderzoek.



Omvangrijk

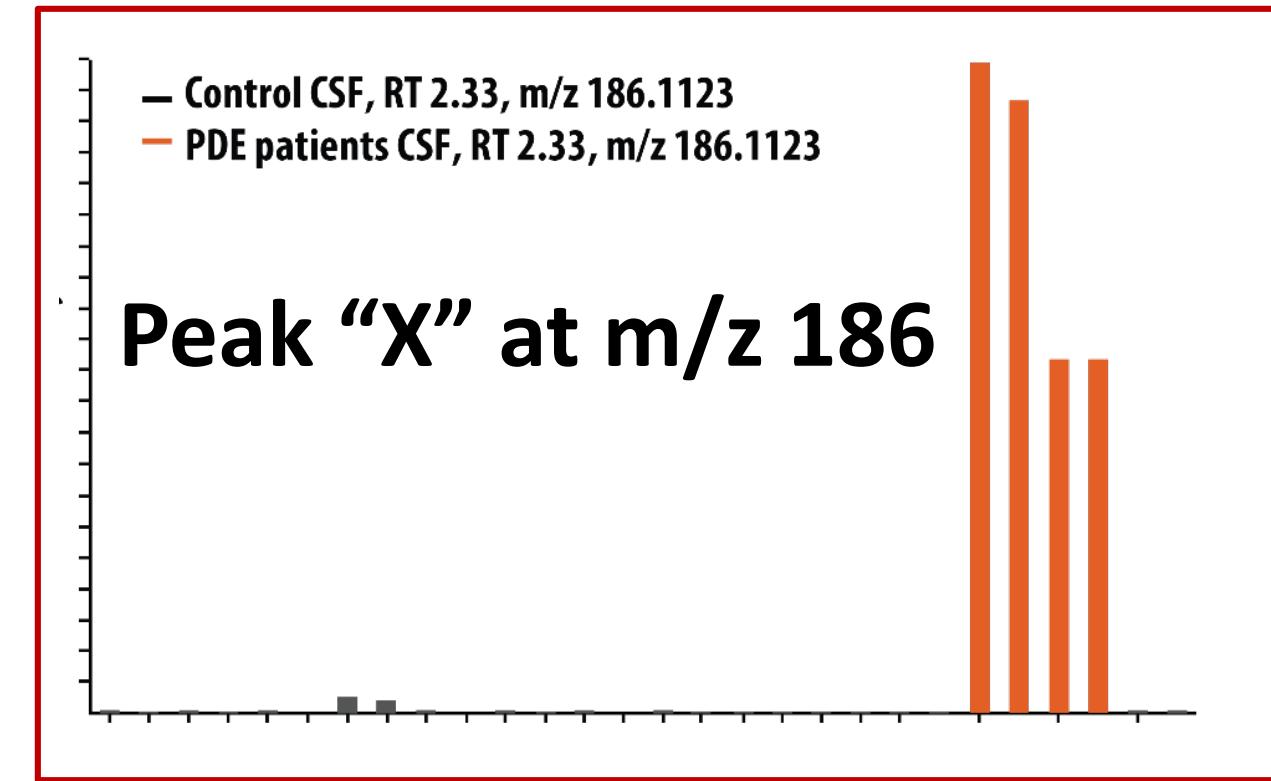
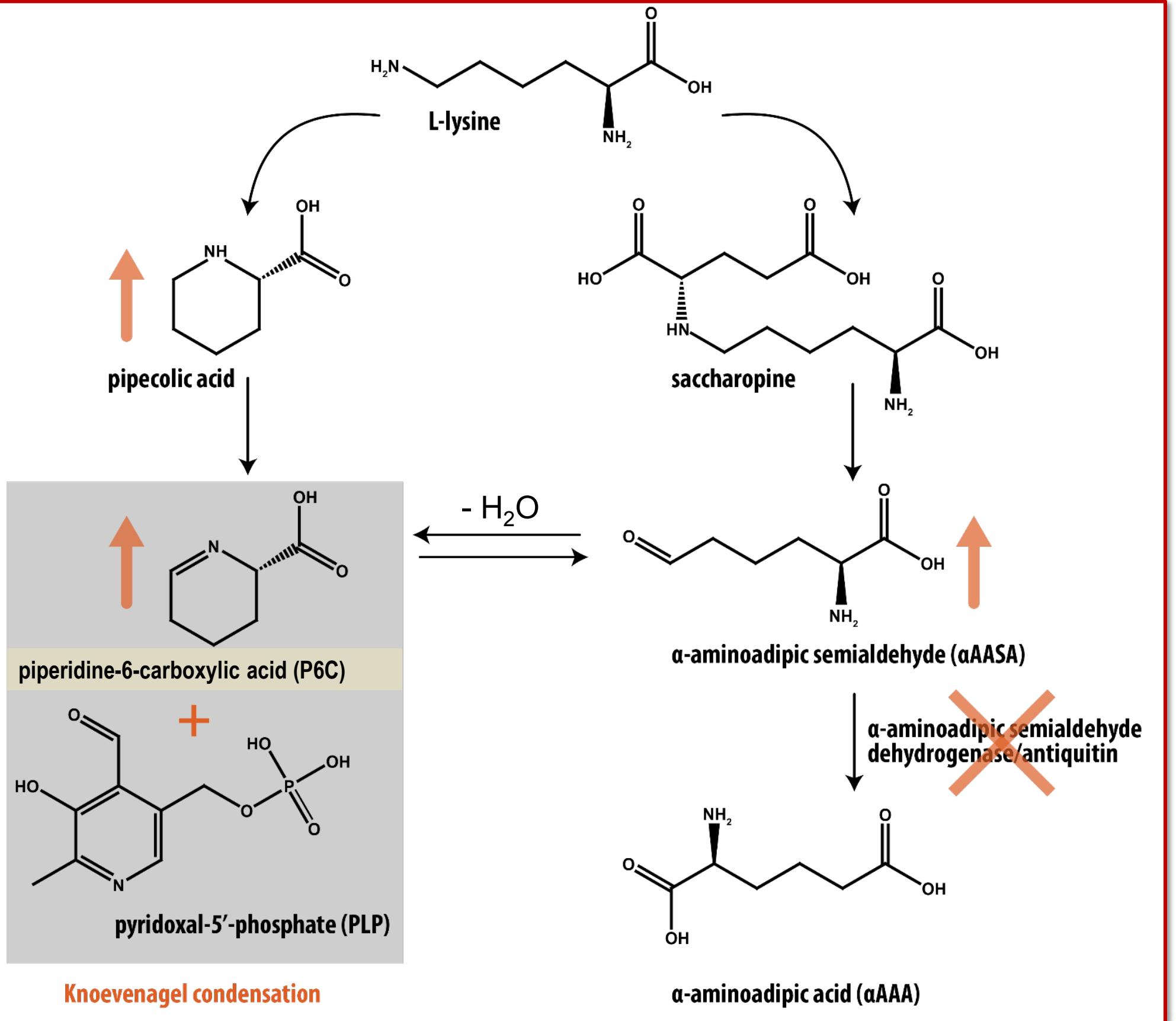
Om de dag wordt in Nederland bij een kind een metabole ziekte gedagnosticert.



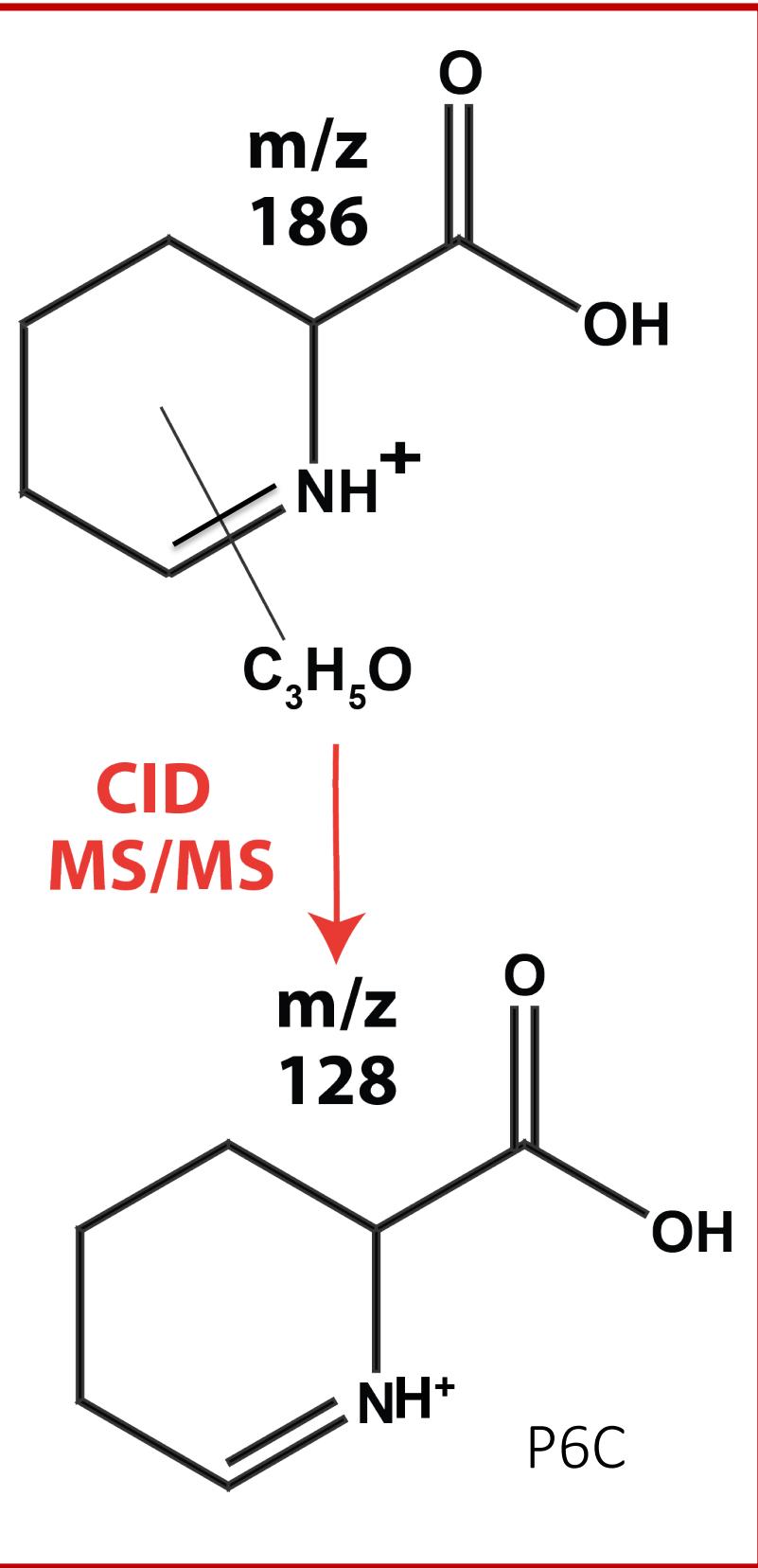
Impact

Metabole ziekten hebben een verwoestend effect op kinderleven en ontwrichten het hele gezin.

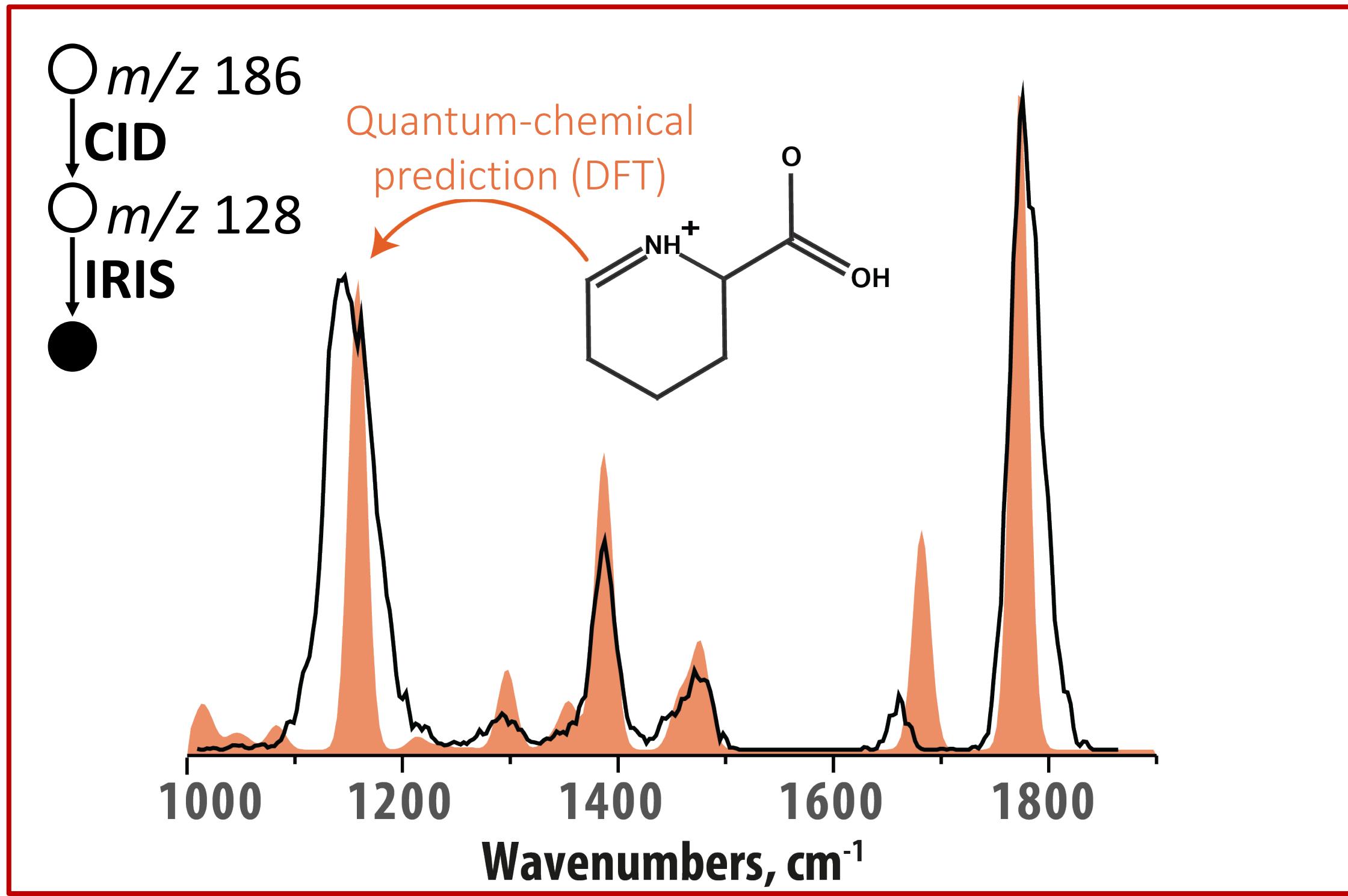
Pyridoxine dependent epilepsy (Antiquitin deficiency)



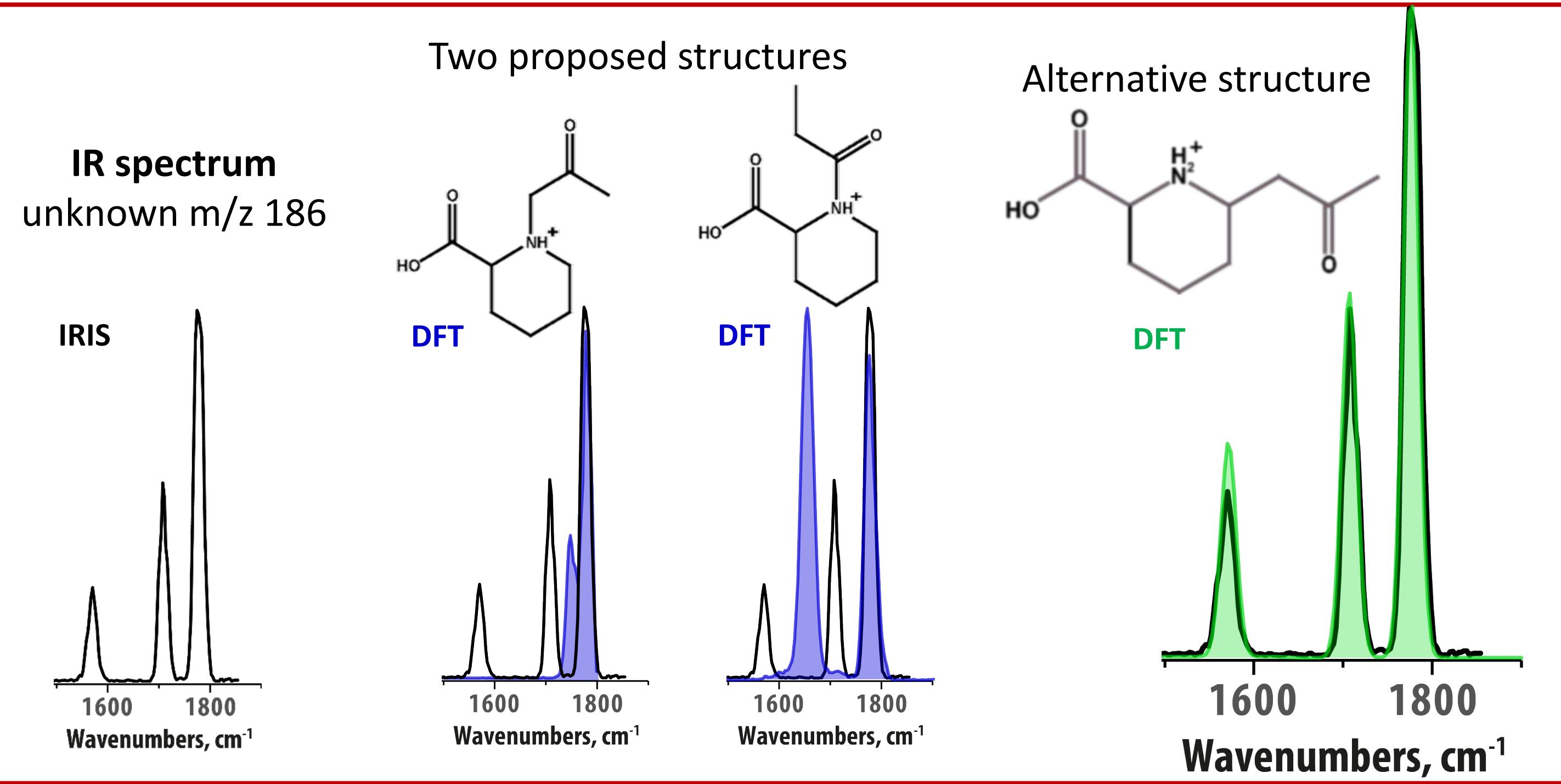
Karlien Coene Leo Kluijtmans Udo Engelke Ron Wevers



IRIS confirms that m/z 128 CID fragment of peak X is P6C



Reference-free identification of an unknown biomarker for PDE



Engelke et al., *J Clin Invest* 2021, 131, e148272

Van Outersterp et al., *Anal Chem* 2021, accepted

drug metabolites

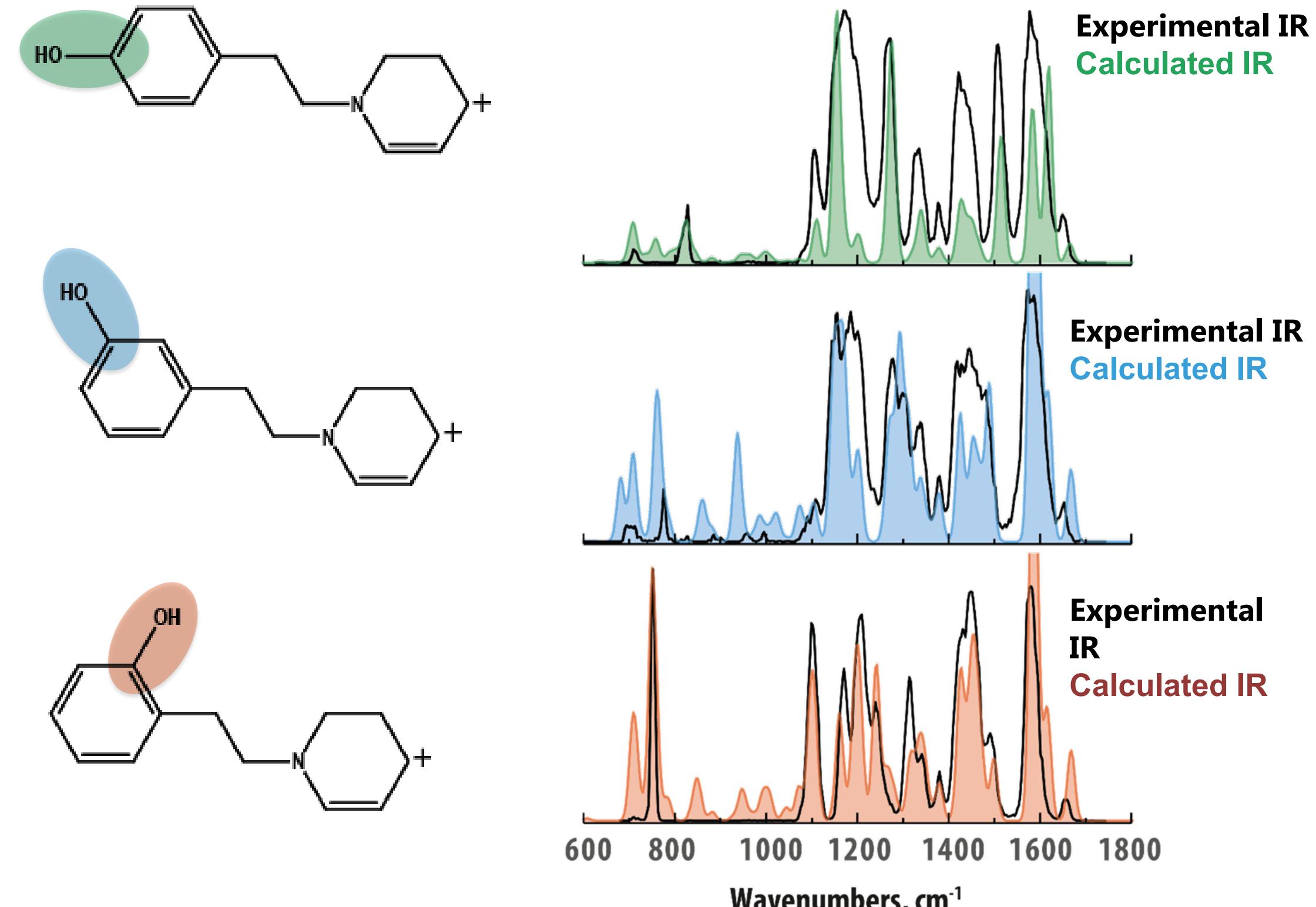
Drug

Hydroxylation

Glucorinidation

Excretion

increasing solubility



Filip Cuyckens
Rob Vreeken



Van Outersterp, Martens, Berden, Koppen, Cuyckens, Oomens, *Analyst* 2020, 145, 6162
Martens, Koppen, Berden, Cuyckens, Oomens, *Anal. Chem.* 2017, 89, 4359

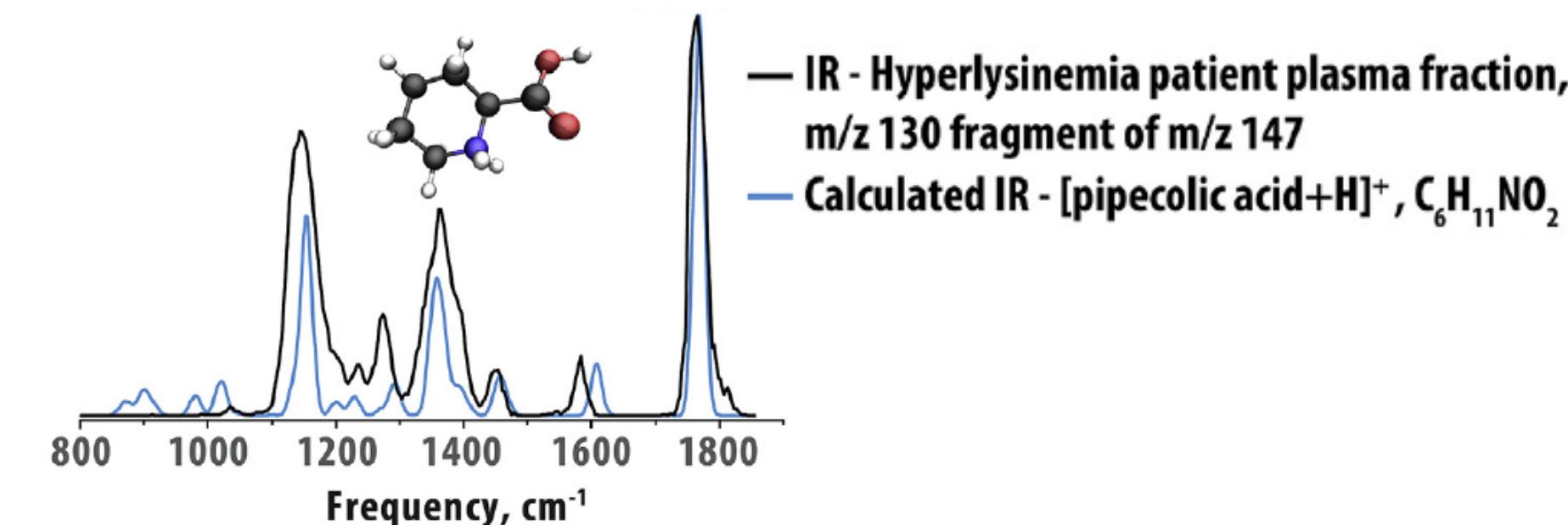
Selected recent applications

METABOLOMICS – Biomarker identification (including LC-MS, CID-MS/MS, DFT)

Infrared ion spectroscopy: New opportunities for small-molecule identification in mass spectrometry - A tutorial perspective

Martens, van Outersterp, Vreeken, Cuyckens, Coene, Engelke, Kluijtmans, Wevers, Buydens, Redlich, Berden, Oomens

Anal. Chim. Acta, 2020, 1093, 1-15

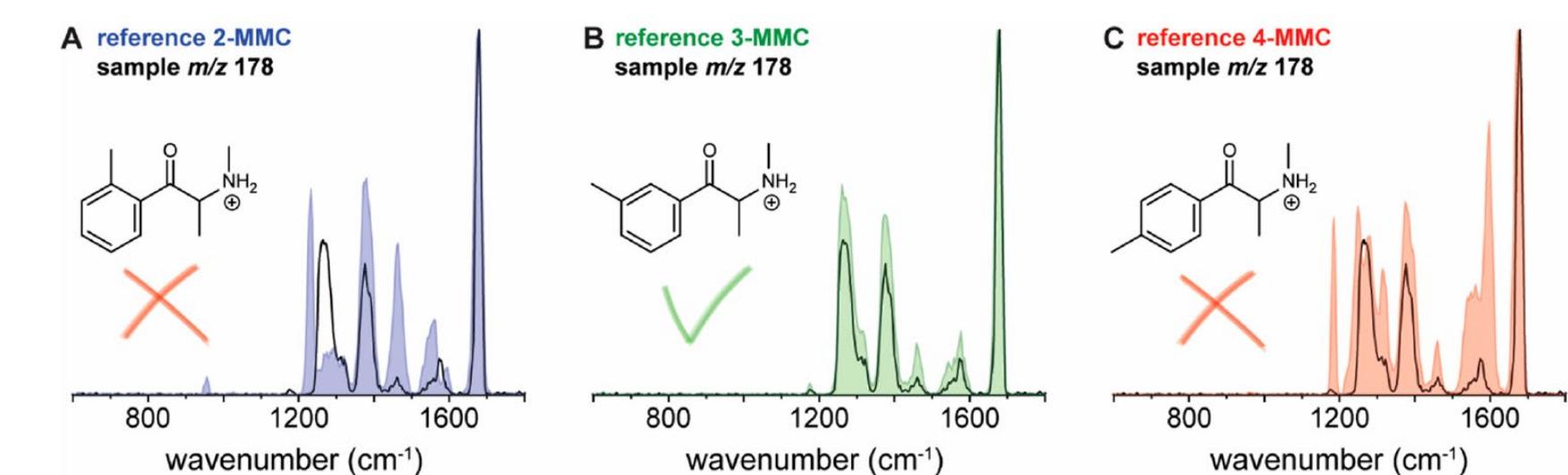


FORENSICS – Identification of psychoactive drugs in confiscated samples

Mass-spectrometry-based identification of synthetic drug isomers using infrared ion spectroscopy

Kranenburg, van Geenen, Berden, Oomens, Martens, van Asten

Anal. Chem. 2020, 92, 7282

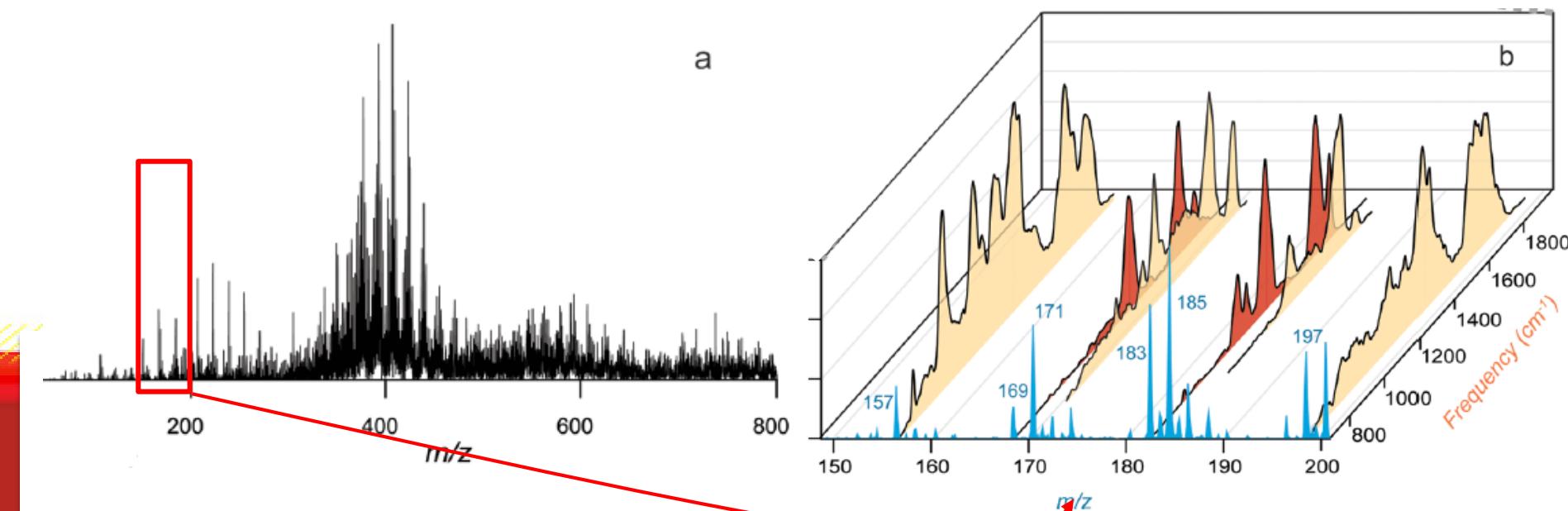


ENVIRONMENTAL – Identification of secondary aerosol constituents

Infrared ion spectroscopy of environmental organic mixtures: probing the composition of alpha-pinene secondary organic aerosol

Walhout, Dorn, Martens, Berden, Oomens, Cheong, Kroll, O'Brien

Environ. Sci. Technol. 2019, 53, 7604-7612



Infrared Ion Spectroscopy (IRIS)

Integration of mass spectrometry and IR spectroscopy

APPLICATIONS

- Sensitivity & selectivity of mass spectrometry
- Molecular structure identification of individual constituents of complex mixtures
- Combine with liquid chromatography (LCMS), collision-induced dissociation (CID MS/MS), MALDI (imaging), ion mobility spectrometry
- Small-molecule (<600 amu), functional groups
- Potential of reference-free identification through quantum chemistry

Infrared ion spectroscopy (IRIS)

Possible applications in synthetic chemistry / fine chemicals

Contaminants / impurities / reaction by-products

- Low abundance, difficult to purify to 0%
- Need to specify identity of remaining impurities
- Guess molecular structure from m/z and starting materials → ref-free ID via QC-IRIS
- Efficient, targeted synthesis of reference standard for impurities

Low-yield products

- Quick check of molecular structure

Medicinal Chemistry

- Drug metabolites
- Biomarker discovery

Reaction intermediates (ionic)

- Aid in fundamental understanding of mechanisms

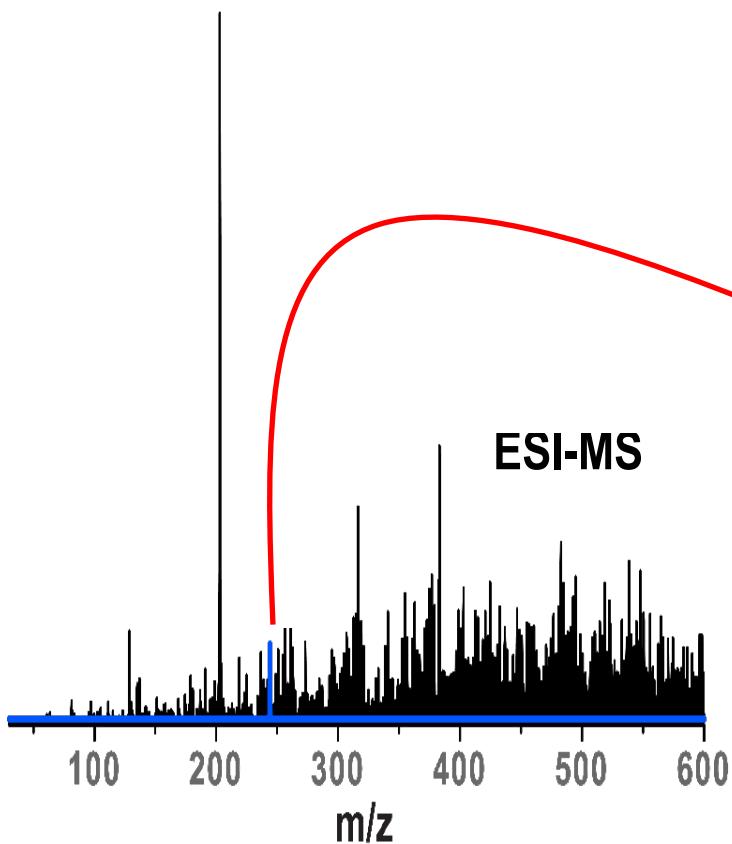
Met dank aan Dr. Thomas Boltje

Infrared Ion Spectroscopy (IRIS)

Integration of mass spectrometry and IR spectroscopy

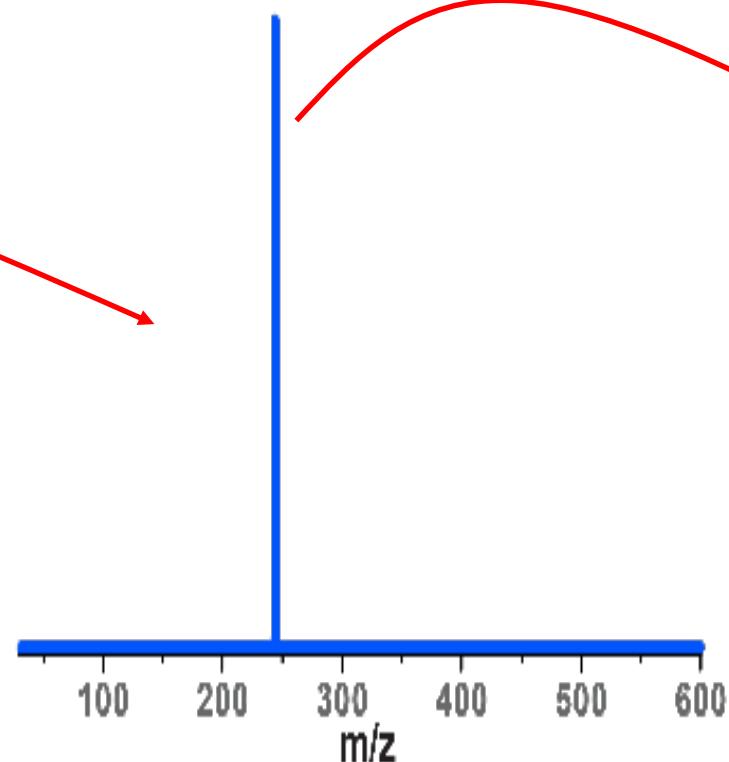
COMPLEX MIXTURE

- urine / plasma
- environmental
- ...



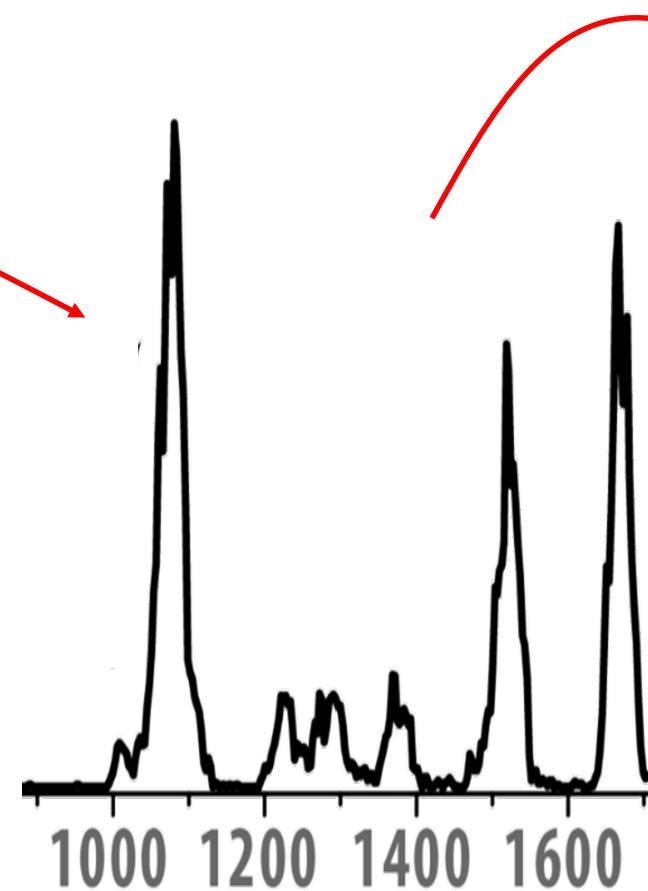
MS/MS

Isolation of single mass peak as in conventional MS/MS analysis



IR ION SPECTROSCOPY

Record IR spectrum directly in mass spectrometer

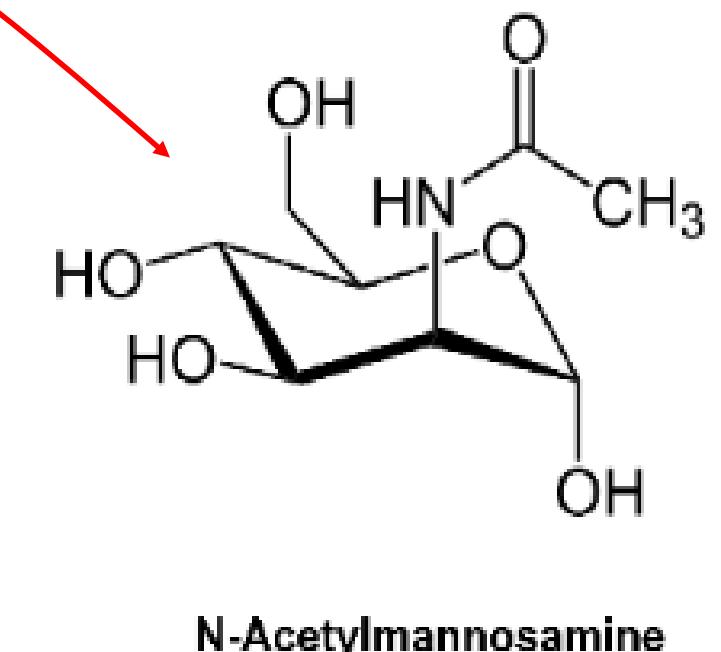


Frequency, cm^{-1}
Infrared spectrum

FELIX laser probes IR spectrum via wavelength-dependent photo-dissociation in ion trap

MOLECULAR STRUCTURE

Vibrational spectrum relates directly to structure



Reference spectrum

Structure identification by comparison with physical or theoretical (DFT) reference spectra

Infrared Ion Spectroscopy (IRIS)

Integration of mass spectrometry and IR spectroscopy



Acknowledgments

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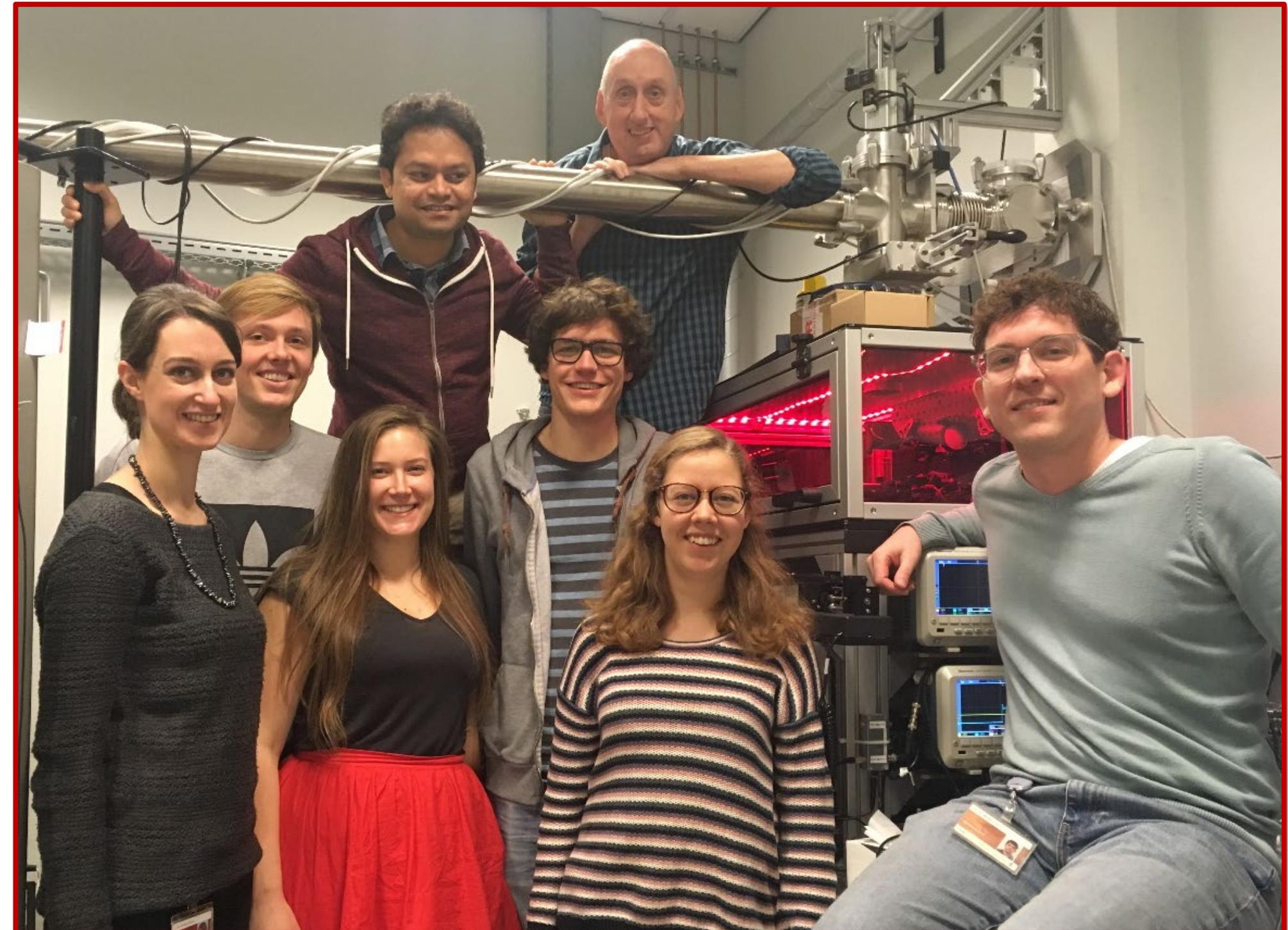
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Filip Cuyckens, Valerie Koppen, Rob Vreeken

(Janssen Pharma)

Thomas Boltje, Floris Rutjes (Org. Chem. RU)



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Britta Redlich

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NWO VICI
NWO TTW



TKI LIFT
NWO Rekentijd
NWO Roadmap



Radboud University

