Use of FTMS in Agrochemicals Research & Development

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Outline

- **Limburgerhof / BASF Crop Protection**
- **Development of new active ingredients (a.i.‘s): role of analytics**
- **Structure elucidation (tasks, approaches, techniques)**
- **Examples:**
  - **Structure elucidation of a goat metabolite (accuracy, resolution)**
  - **Structure elucidation of minor components; unusual molecular ion cluster (accuracy)**
  - **Structure elucidation of minor components; fragmentation (IRMPD)**

Agricultural Center Limburgerhof

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Development of a Crop Protection Active Ingredient

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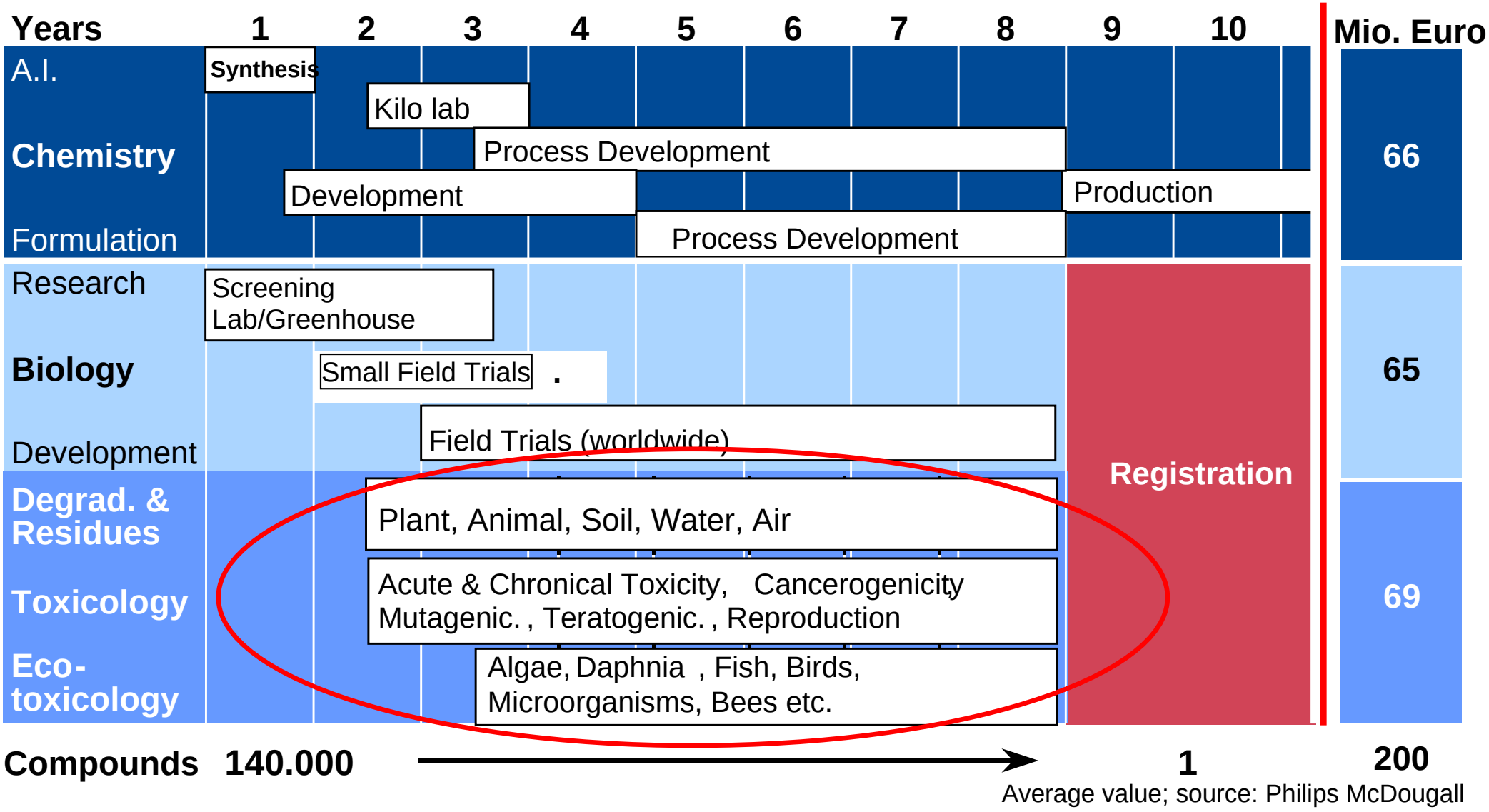


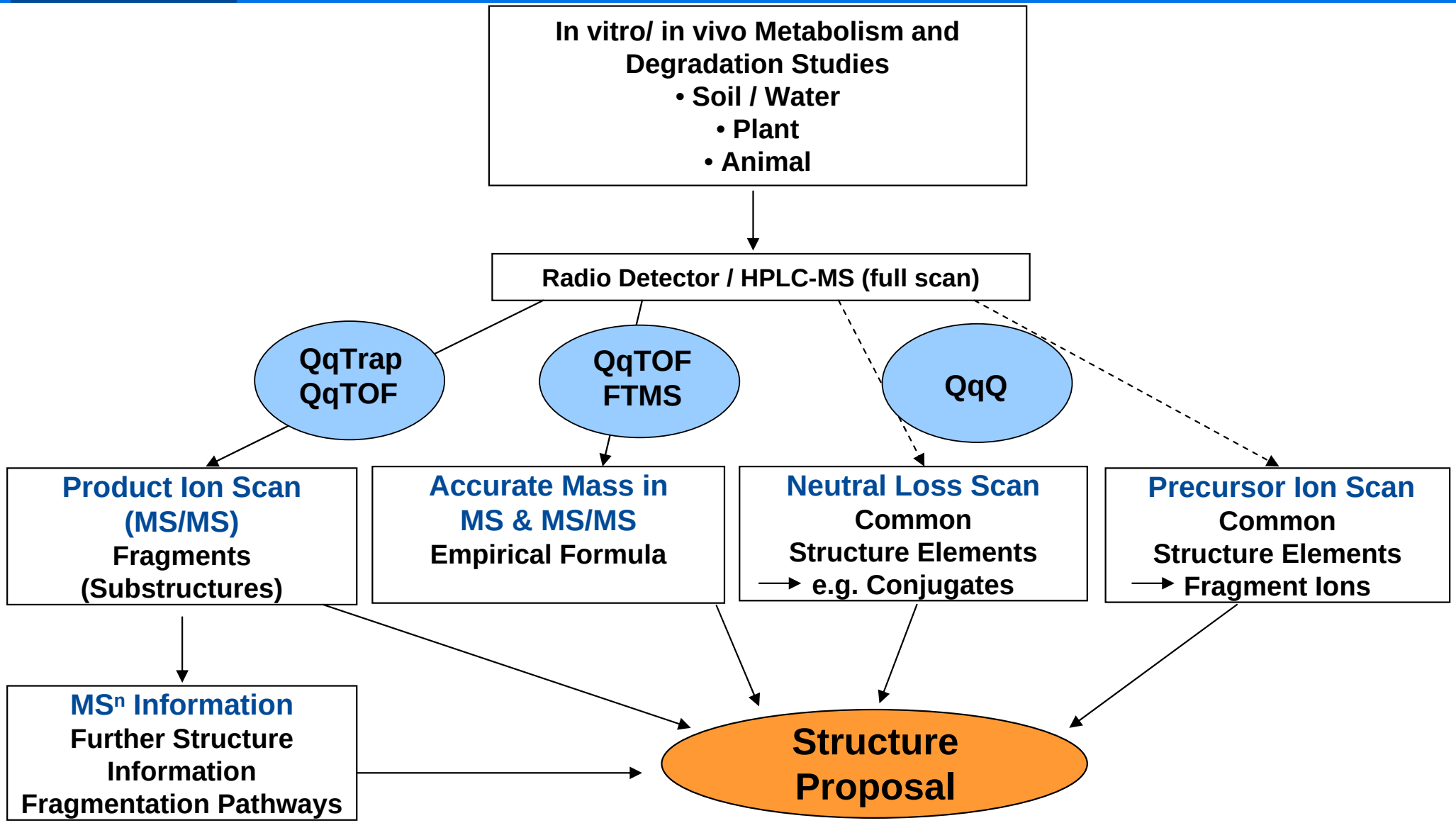
Average value; source: Philips McDougall

Structure Elucidation Crop Protection Tasks

- **Structure confirmation (MS, NMR, IR)**
  - **Reference substances** — **GLP**
  - **Radio synthesis (^{14}C)** — **GLP**
  - **Known metabolites** — **GLP**
- **Structure elucidation (MS, NMR)**
  - **Metabolites in plant, animal, soil (^{14}C)** — **GLP**
  - **Hydrolysis and photolysis products (^{14}C)** — **GLP**
  - **Minor components**
  - **Formulants, ……**

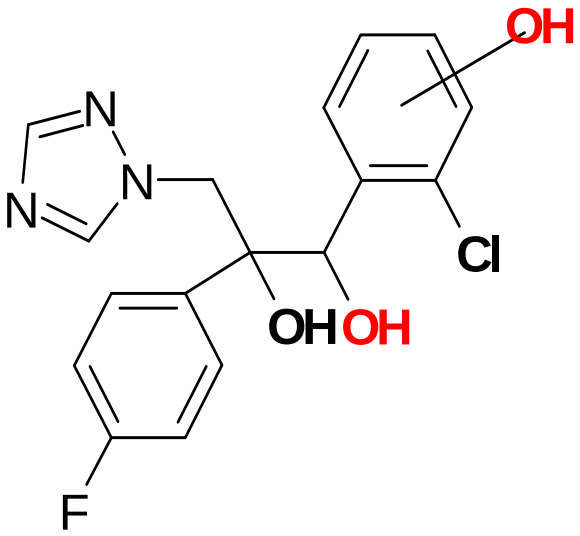
2008: > 1500 Samples
> 2500 Reported structures

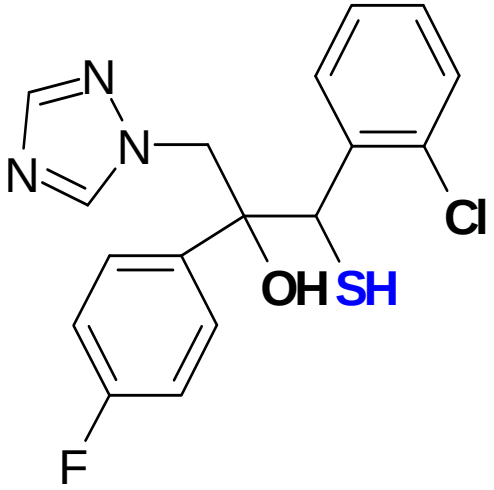
Structure Elucidation Technologies



1. Epoxiconazole Goat Metabolite Problem

M = 363





$C_{17}H_{15}N_3O_3FCl$?

$C_{17}H_{15}N_3OFSCl$?

1. Epoxiconazole Goat Metabolite Chromatograms (+ESI FTMS)

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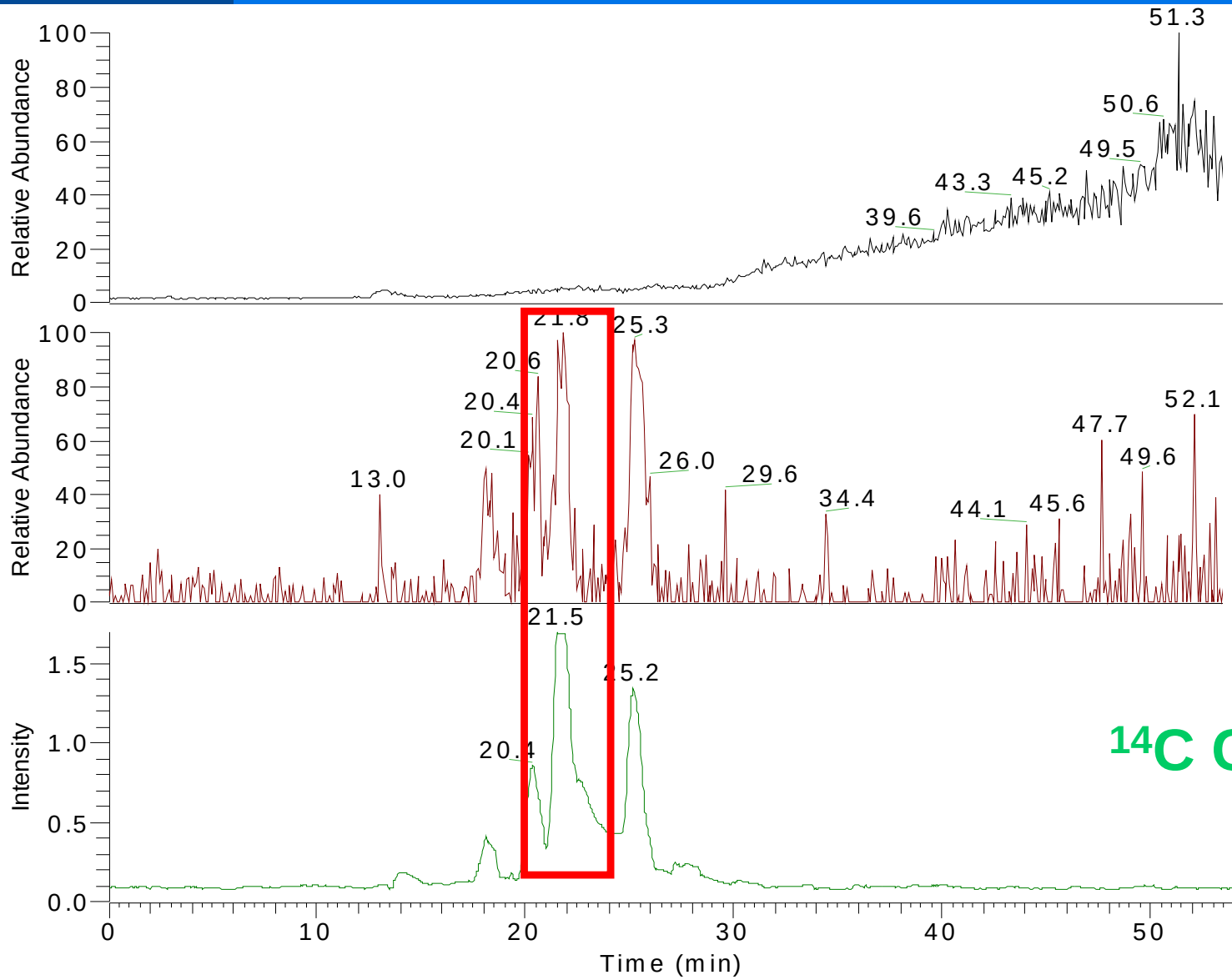
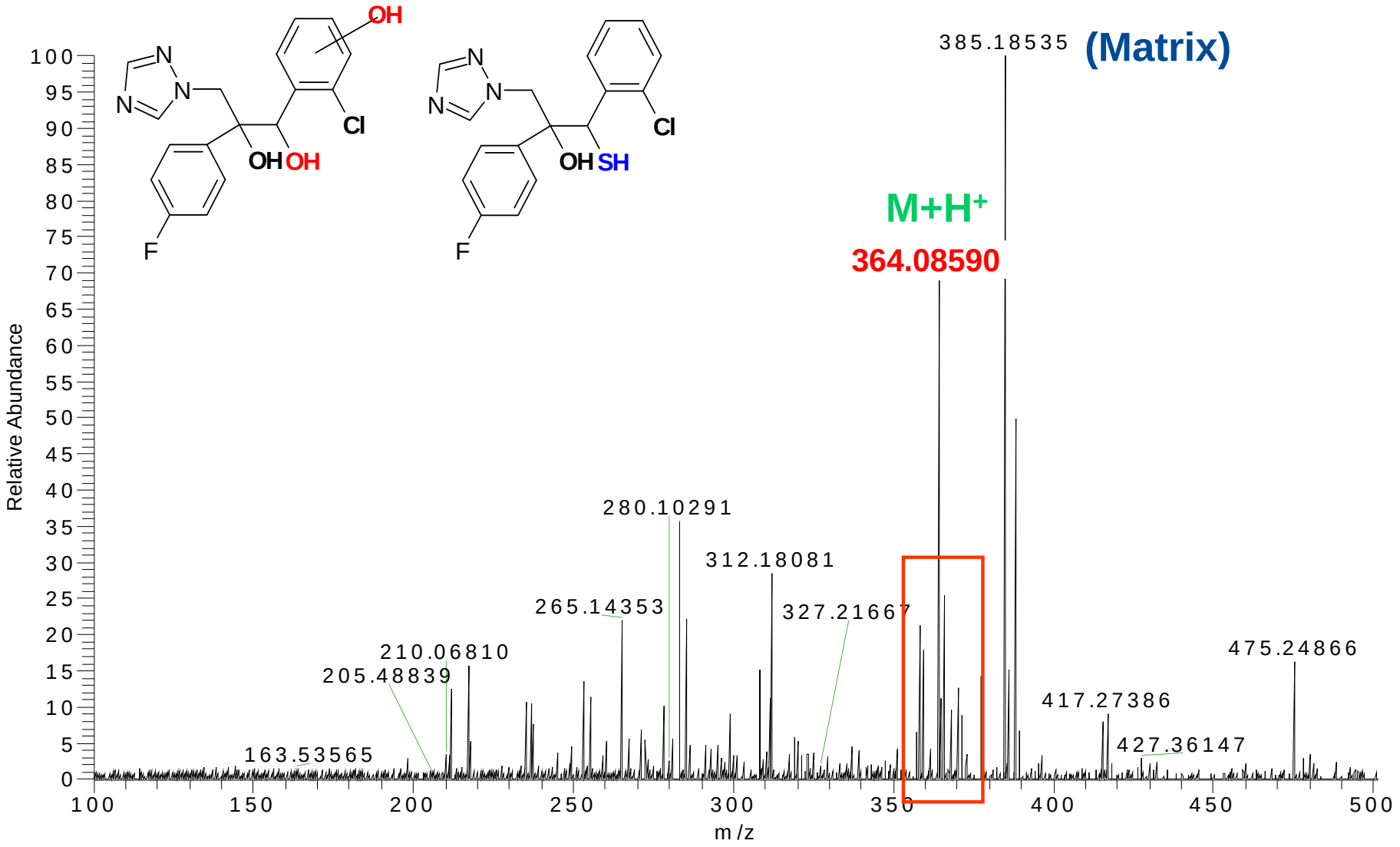


TIC (FT-MS)

EIC *m/z* 364

^{14}C Chromatogram

1. Epoxiconazole Goat Metabolite Full Scan Mass Spectrum (+ESI FTMS)



1. Epoxiconazole Goat Metabolite Calculation of Empirical Formula

- **QqTOF: $[M+H^+]_{exp.}$: 364.0907**
- **FT-MS: $[M+H^+]_{exp.}$: 364.08590**
- **Limitations:**
  - **C: 0-50**
  - **H: 0-50**
  - **F: 0-1**
  - **Cl: 0-1**
  - **N: 0-5**
  - **O: 0-3**
  - **S: 0-1**

$C_{17}H_{15}N_3O_3FCl \overset{?}{\Longleftrightarrow} C_{17}H_{15}N_3OFSCl$

1. Epoxiconazole Goat Metabolite Results TOF

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< 2 ppm
< 5 ppm

< 10 ppm

	Formular	Calculated m/z (u)	mu Error	PPM Error	DBE
1	C20 H15 N3 O F S	364,0914	-0,6387	-1,7543	14,5
2	C22 H16 N O F Cl	364,0898	0,9033	2,481	14,5
3	C14 H20 N3 O3 F S Cl	364,0892	1,554	4,2683	5,5
4	C19 H20 N O F S Cl	364,0932	-2,4686	-6,7802	9,5
5	C17 H19 N3 O2 S Cl	364,0881	2,6969	7,4074	9,5
6	C23 H11 N3 O F	364,088	2,7332	7,5069	19,5
7	C15 H15 N5 O3 F S	364,0874	3,3839	9,2942	10,5
8	C18 H14 N5 O2 S	364,0862	4,5268	12,4334	14,5
9	**C17 H16 N3 O3 F Cl**	**364,0858**	**4,926**	**13,5296**	**10,5**
10	C19 H15 N5 O Cl	364,0959	5,1644	-14,1844	14,5
11	C24 H14 N O3	364,0968	-6,0199	-16,534	18,5
12	C20 H15 N3 O2 Cl	364,0847	6,0689	16,6687	14,5
13	C16 H16 N5 O2 F Cl	364,0971	-6,3073	-17,3235	10,5
14	C18 H11 N5 O3 F	364,084	6,7559	18,5555	15,5
15	C21 H10 N5 O2	364,0829	7,8988	21,6947	19,5
16	C16 H19 N5 O S Cl	364,0993	-8,5363	-23,4457	9,5
17	C21 H18 N O3 S	364,1001	-9,3918	-25,7953	13,5
18	C13 H20 N5 O2 F S Cl	364,1004	-9,6793	-26,5848	5,5
19	C21 H15 N O2 F S	364,0802	10,5946	29,0988	14,5
20	C24 H14 N O S	364,079	11,7375	32,2379	18,5

$C_{17}H_{15}N_3O_3FCl$? $C_{17}H_{15}N_3OFSCl$

1. Epoxiconazole Goat Metabolite Results FT-MS

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< 2 ppm

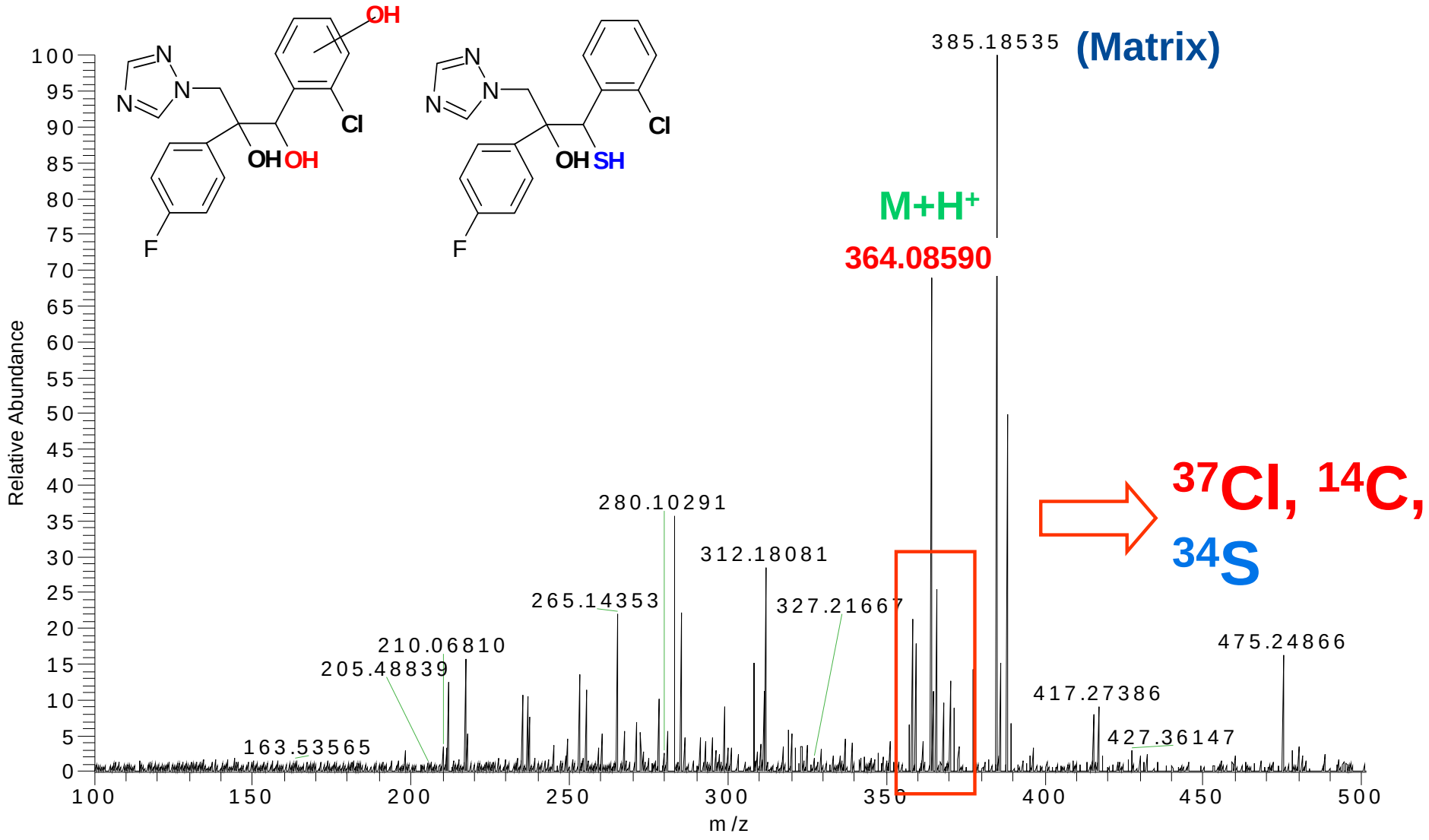
< 5 ppm

< 11 ppm

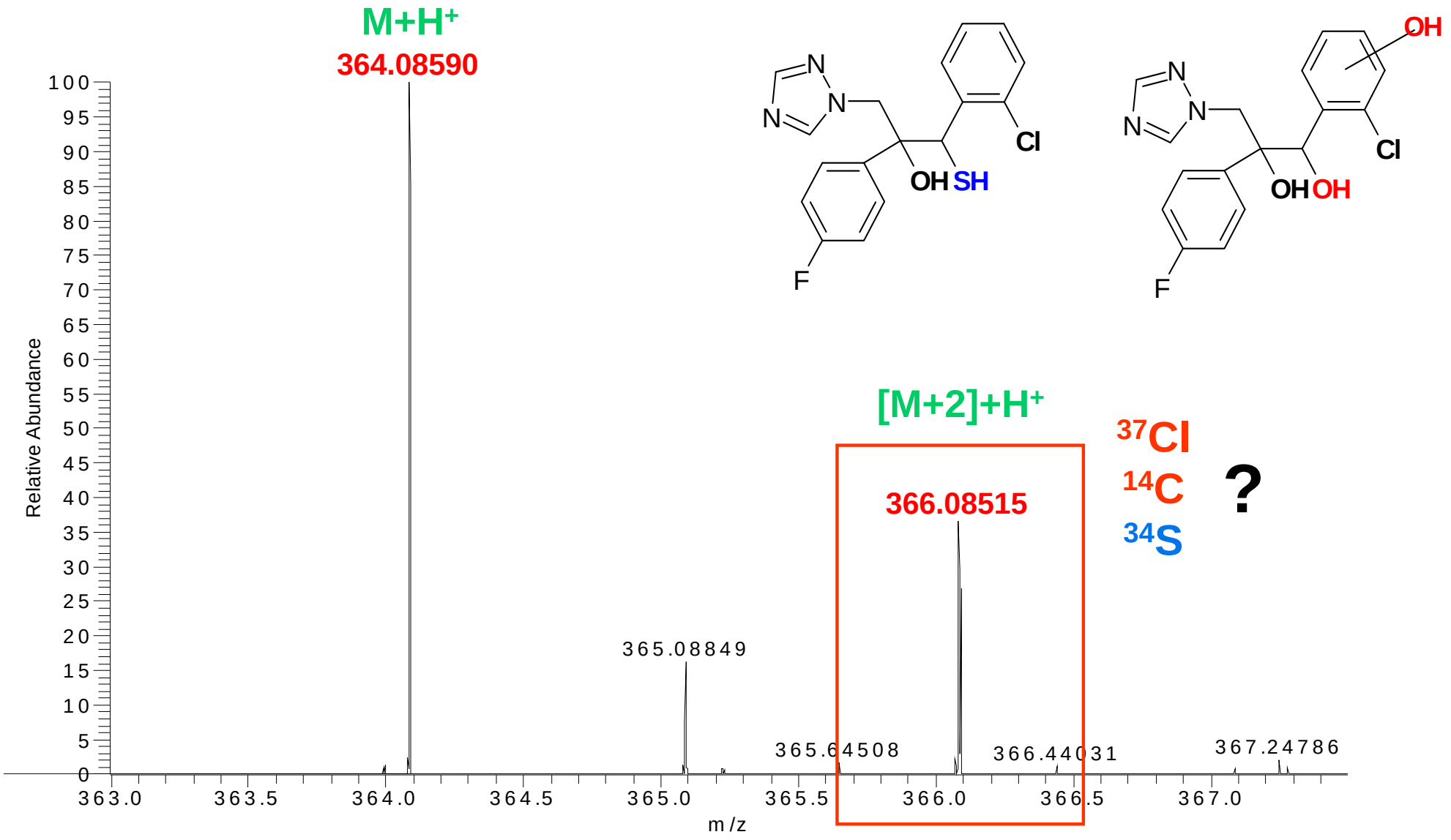
	Formular	Calculated m/z (u)	mu Error	PPM Error	DBE
1	**C17 H16 N3 O3 F Cl**	**364,0858**	**0,026**	**0,0714**	**10,5**
2	C18 H14 N5 O2 S	364,0862	-0,3731	-1,0247	14,5
3	C20 H15 N3 O2 Cl	364,0847	1,1689	3,2106	14,5
4	C15 H15 N5 O3 F S	364,0874	-1,516	-4,1639	10,5
5	C18 H11 N5 O3 F	364,084	1,8559	5,0974	15,5
6	C23 H11 N3 O F	364,088	-2,1667	-5,9512	19,5
7	C17 H19 N3 O2 S Cl	364,0881	-2,203	-6,0507	9,5
8	C21 H10 N5 O2	364,0829	2,9988	8,2366	19,5
9	C14 H20 N3 O3 F S Cl	364,0892	-3,3459	-9,1899	5,5
10	C22 H16 N O F Cl	364,0898	-3,9966	-10,9773	14,5
11	C20 H15 N3 O F S	364,0914	-5,5387	-15,2126	14,5
12	C21 H15 N O2 F S	364,0802	5,6946	15,6409	14,5
13	C24 H14 N O S	364,079	6,8375	18,78	18,5
14	C19 H20 N O F S Cl	364,0932	-7,3686	-20,2387	9,5
15	C18 H19 N O3 S Cl	364,0768	9,0303	24,8027	9,5
16	C24 H11 N O2 F	364,0768	9,0666	24,9023	19,5
17	C19 H15 N5 O Cl	364,0959	-10,0644	-27,6429	14,5
18	C19 H14 N3 O3 S	364,075	10,8602	29,8288	14,5
19	C24 H14 N O3	364,0968	-10,9199	-29,9926	18,5
20	C16 H16 N5 O2 F Cl	364,0971	-11,2073	-30,7821	10,5

$C_{17}H_{15}N_3O_3FCl$? $C_{17}H_{15}N_3OFSCl$

1. Epoxiconazole Goat Metabolite Full Scan Mass Spectrum (+ESI FTMS)

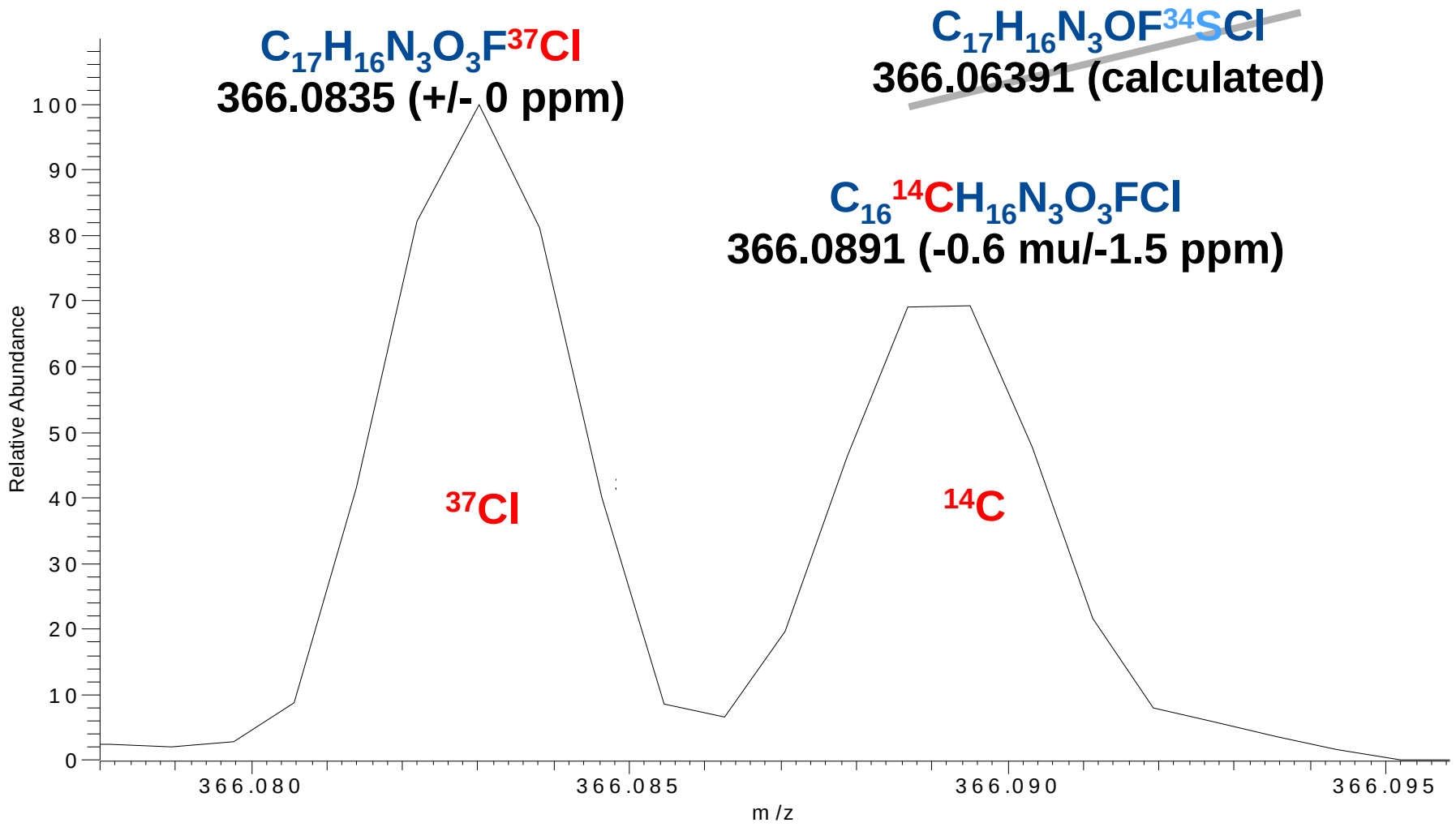


1. Epoxiconazole Goat Metabolite [M+2]+H+ Peak

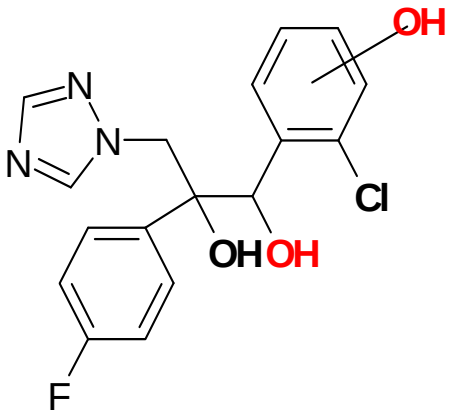


1. Epoxiconazole Goat Metabolite Resolved [M+2]+H⁺ Peak

Resolution = *m* / Δ*m* = 366.08515 / 0.0056 = 65 370



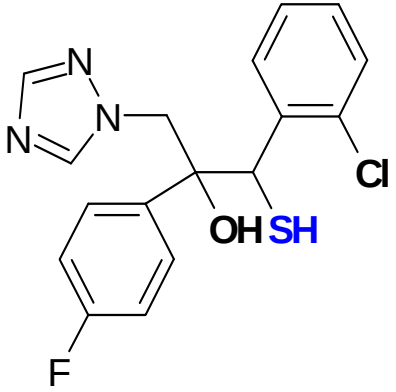
1. Epoxiconazole Goat Metabolite Conclusion



YES

$C_{17}H_{15}N_3O_3FCl$ $\overset{?}{\Longleftrightarrow}$ $C_{17}H_{15}N_3OFSCl$

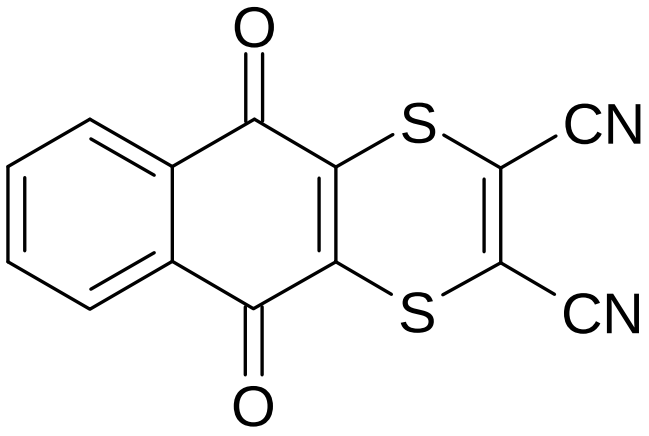
M = 363



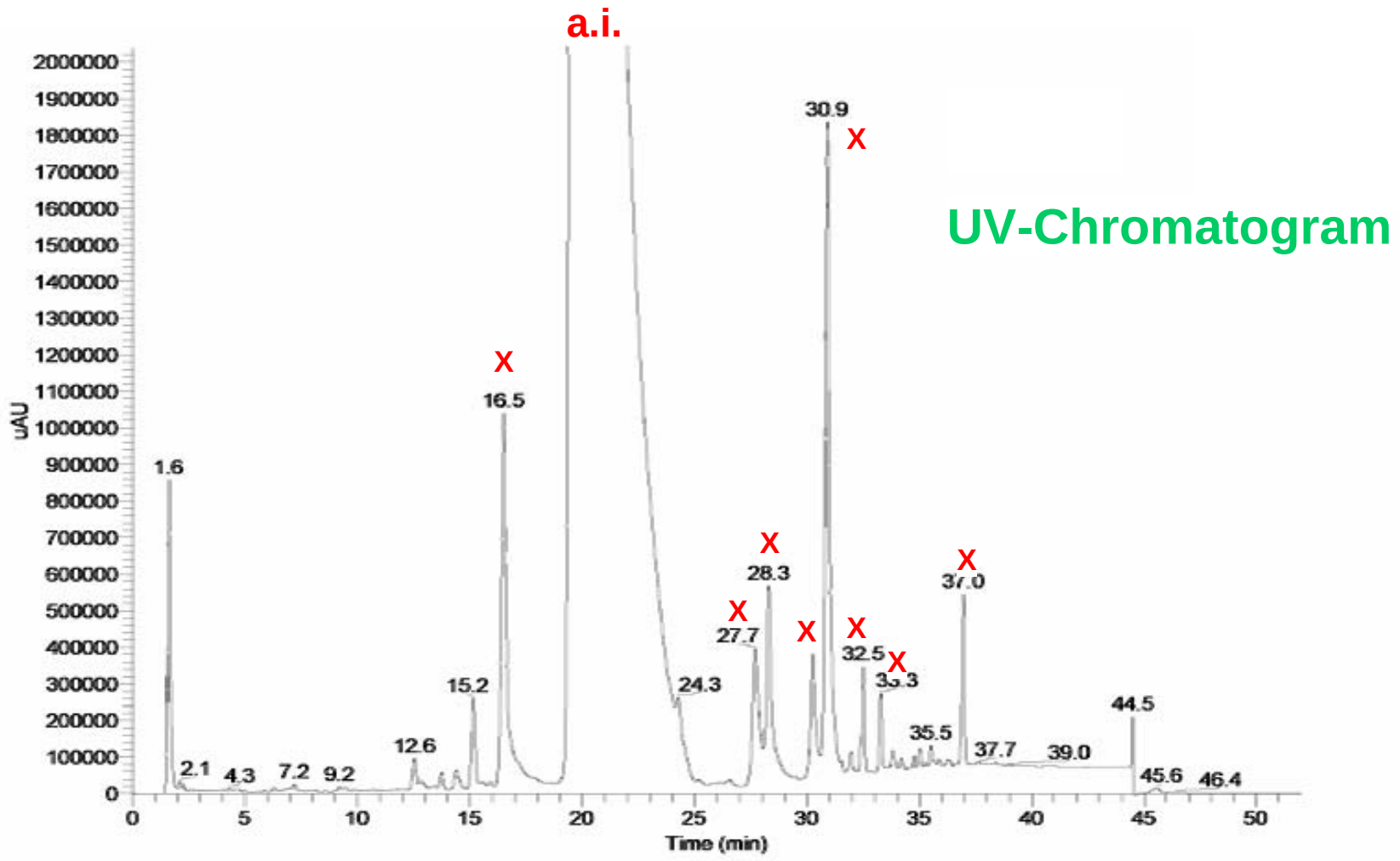
NO

2. Dithianon
Unusual molecular ion cluster in -ESI

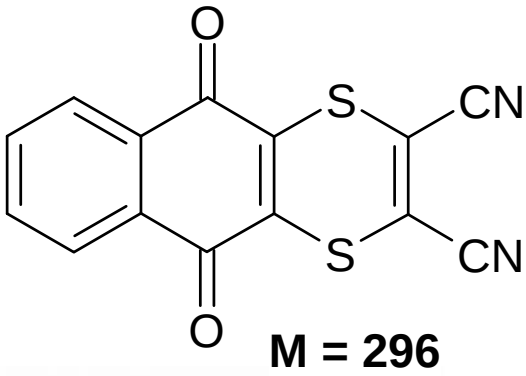
- Fungicide
- Task: structure elucidation of minor components
- Unusual molecular ion cluster („isotope pattern“) in -ESI requires additional MS experiments
  - ESI (pos/neg)
  - APCI (pos/neg)
  - APPI (pos/neg)



2. Dithianon
UV chromatogram of technical a.i.



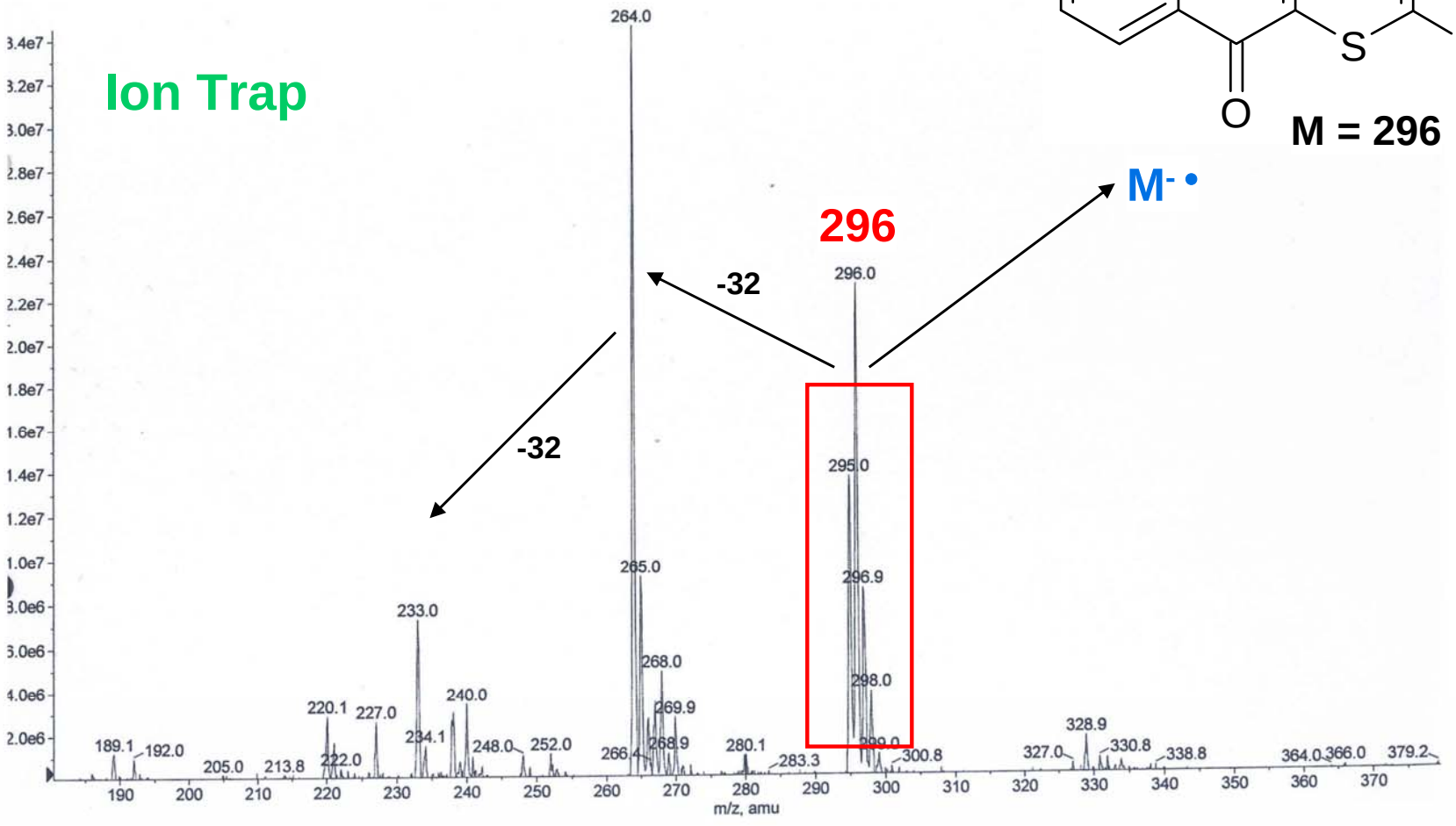
2. Dithianon
- ESI (IonTrap)



M = 296

-ESI

Ion Trap



2. Dithianon
- ESI (FT-ICR)

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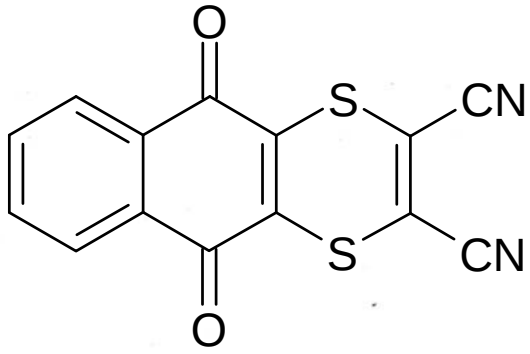
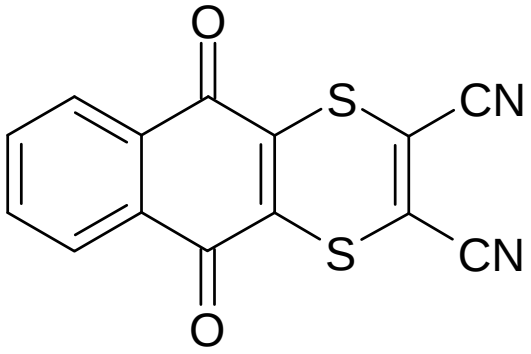
- ESI

FTMS



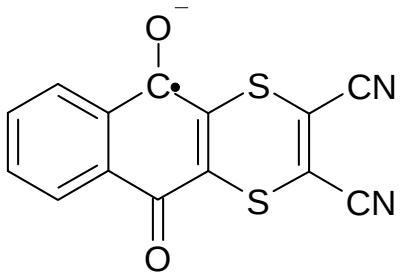
M = 296

2. Dithianon
- ESI: Origin of $[M+H]^-$



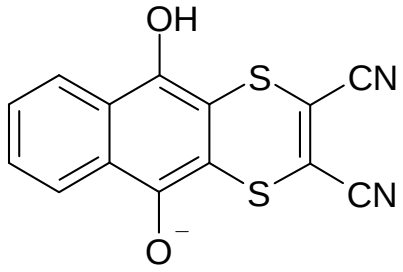
M = 296

+e⁻



$M^{-\bullet}$ *m/z* 296

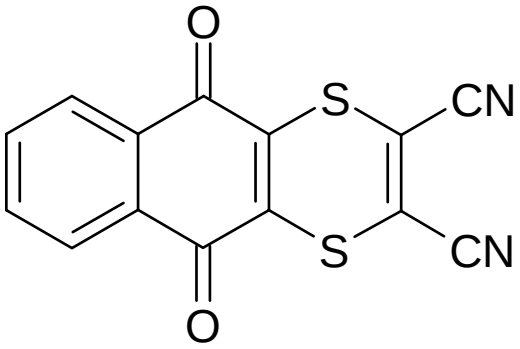
H-X (solvent)
- X•



$[M+H]^-$ *m/z* 297

2. Dithianon
Unusual Quasi Molecular Ions only in -ESI

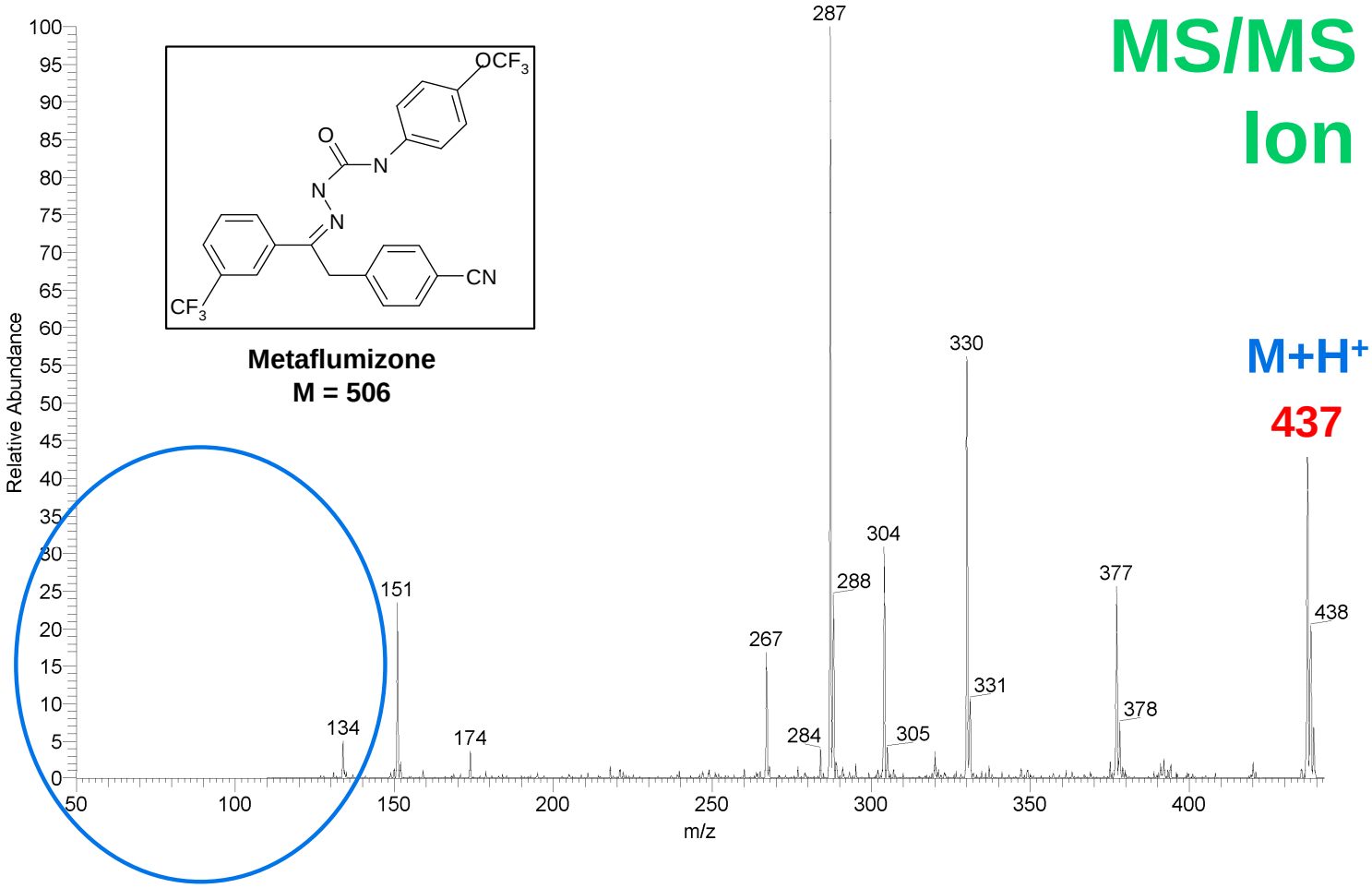
ESI	APCI	APPI
■ pos. mode ➢ $M^{+\bullet}$	■ pos. mode ➢ $M^{+\bullet}$	■ pos. mode ➢ $M^{+\bullet}$
■ neg. mode ➢ $[M-H]^-$, $M^{-\bullet}$, $[M+H]^-$	■ neg. mode ➢ $M^{-\bullet}$	■ neg. mode ➢ $M^{-\bullet}$



2. Dithianon
Conclusion

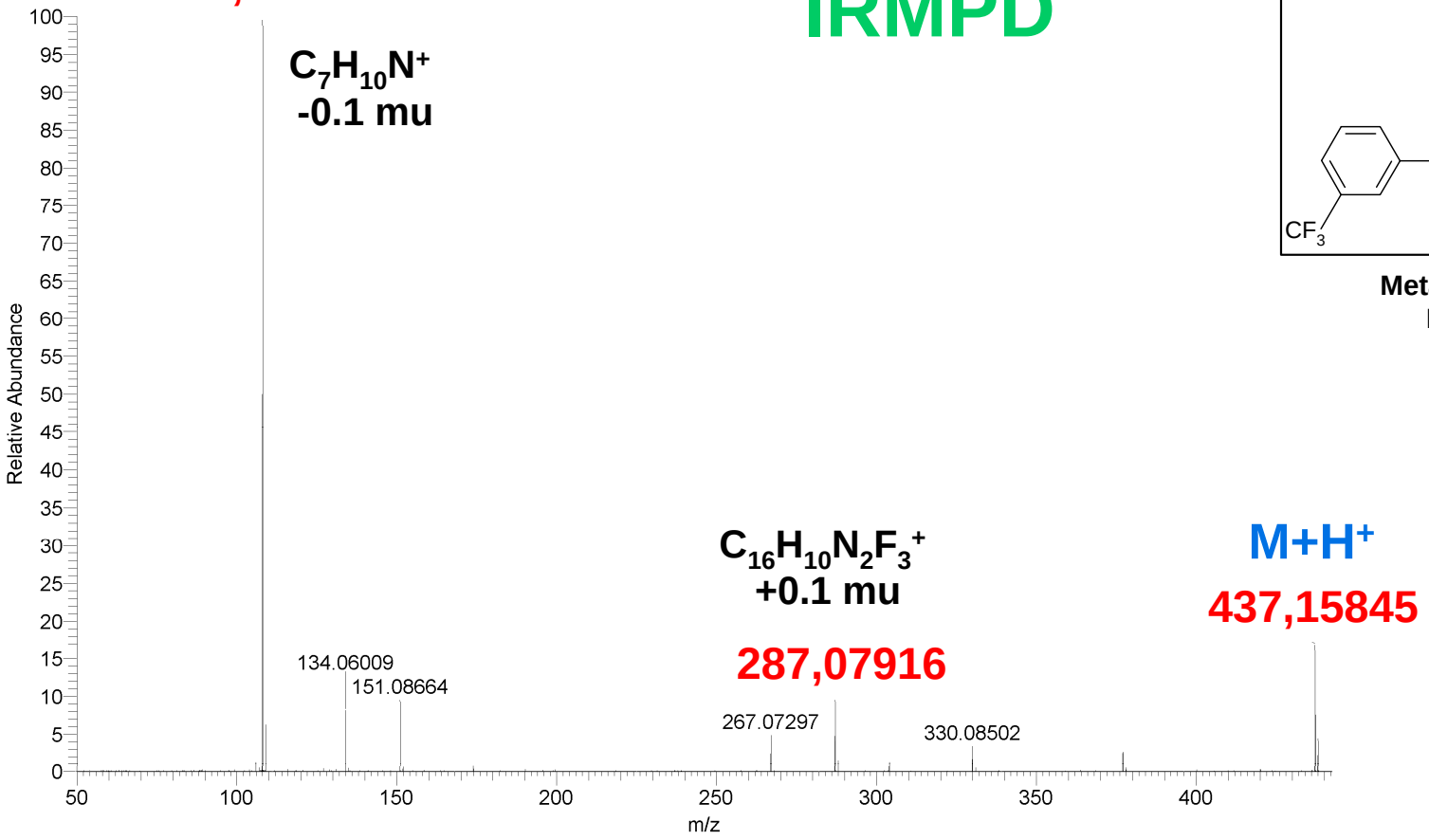
- For interpretation of quasi molecular ions positive and negative mode data are helpful
- Formation of radical cations and - anions in pos./neg. mode ($M^{+\cdot}$, $M^{-\cdot}$) by all applied ionization techniques (ESI, APCI, APPI)
- Negative mode APCI is most sensitive for detection of Dithianon and minor components
- +/- ESI is standard ionization method for our applications
- Unusual molecular ion cluster in neg. mode ESI
- Identification of $[M+H]^-$ quasi molecular ions by accurate mass measurement (FTMS)

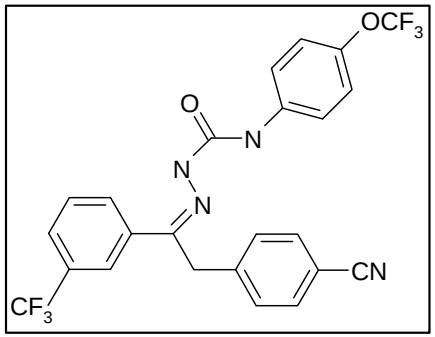
3. Metaflumizone Minor Component Ion Trap Fragmentation



3. Metaflumizone Minor Component IRMPD (FTMS)

MS/MS *m/z* 437 IRMPD





Metaflumizone
M = 506

Conclusion

- **Determination of accurate mass -> empirical formula for analyte molecule and fragments**
- **Ultra high resolution gives additional information about elemental composition**
- **MS/MS fragmentation by IRMPD even in low mass range**
- **LTQ-FTMS is a powerful tool for structure elucidation in agrochemicals research & development**