

Investigation of the Impurities in Dronabinol Samples by LC/MS

Authors: Huahua Jian, Isil Dilek, Uma Sreenivasan, Kenan Yaser

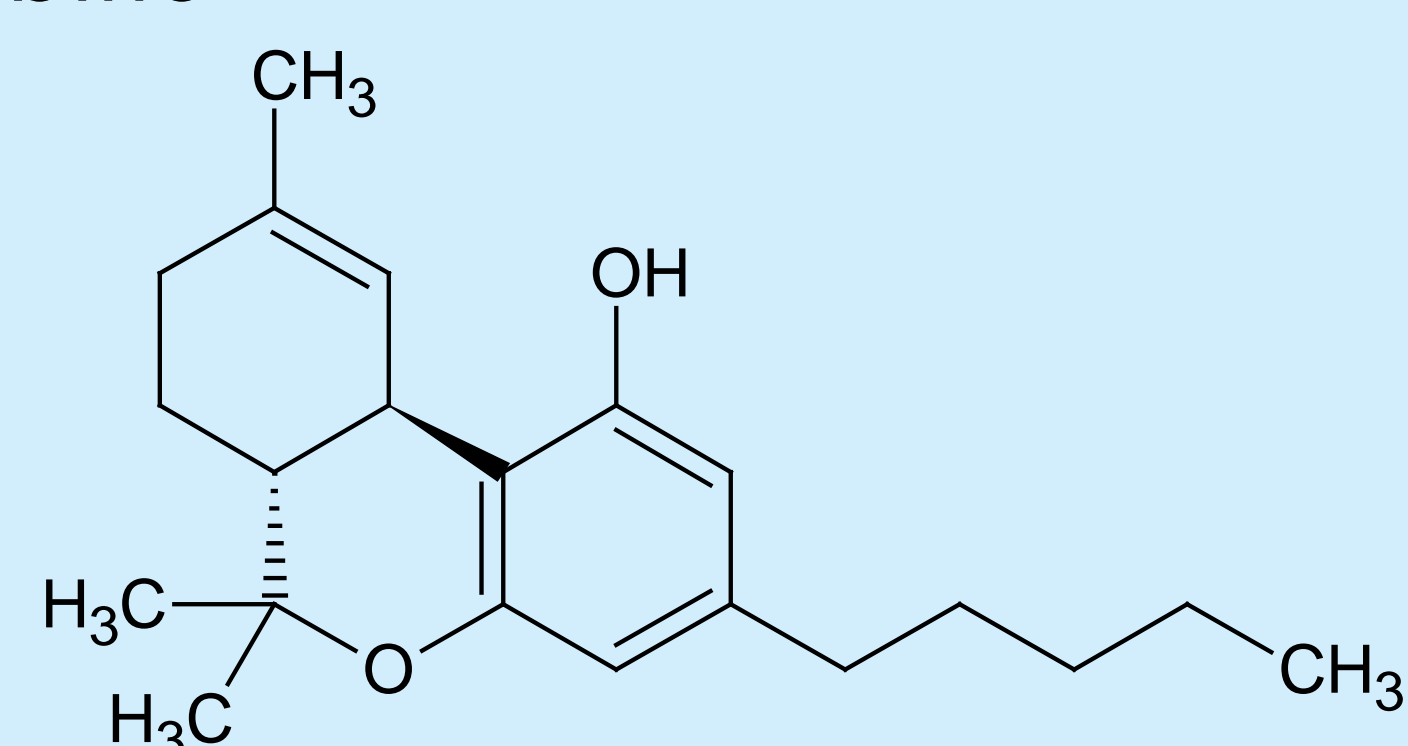
Introduction

Tetrahydrocannabinol (Δ^9 -THC) is a psychoactive substance found in cannabis plants ("Medical Marijuana"). Synthetic Δ^9 -THC, also called Dronabinol, was approved by US FDA as a drug to treat pain, anorexia and nausea related to chemotherapy and other disorders.

Dronabinol is a light yellow to amber glassy material. It is sensitive to light, heat, and oxygen (air). The impurities in commercial Dronabinol drugs may come from either the synthetic process or through product degradation. Identification of these impurities is required by FDA and ICH guidelines for pharmaceuticals.

A comparison of impurities in Dronabinol from a variety of sources was performed by HPLC and LCMS.

Dronabinol



Materials and Methods

Materials

- Austin Pharma API, Dronabinol, USP
- Capsules manufactured from Austin Pharma API
- Marinol® (RLD)
- Generic Dronabinol manufactured by Par Pharmaceuticals

Methods

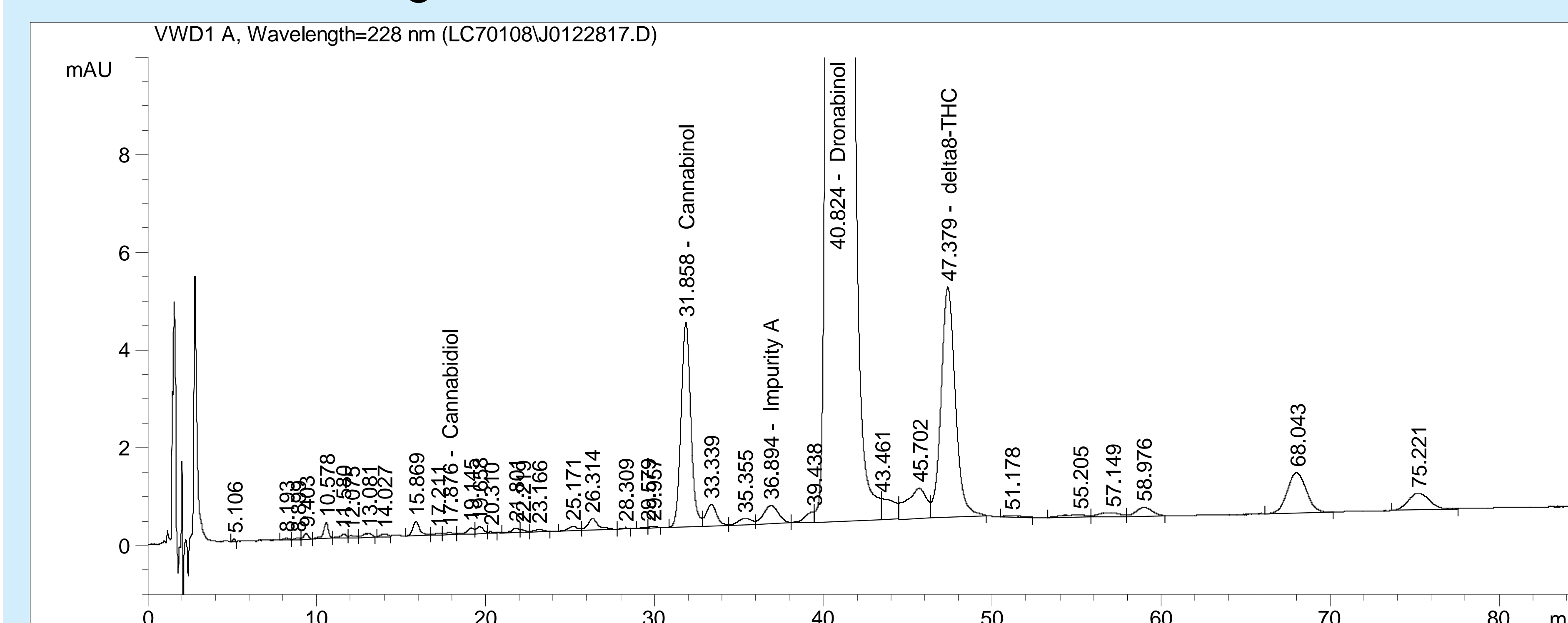
HPLC method conditions are based on USP 29 monograph for Dronabinol. LCMS run conditions were adapted from the HPLC method using ammonium formate as the mobile phase additive for MS detection.

Capsules were extracted based on USP Dronabinol capsule monograph.

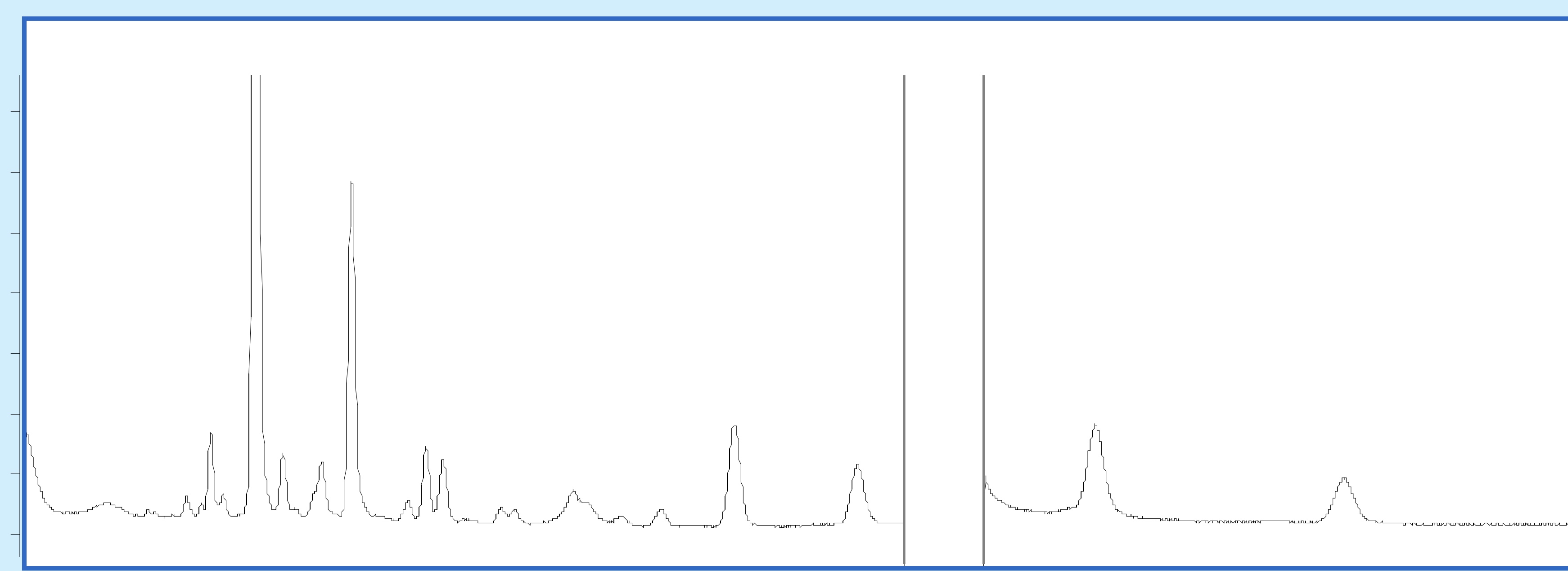
| | |
|---------------------|---|
| Instrument | Agilent G6410 Series Triple Quad (QQQ) LC/MS/MS |
| Column | Phenomenex Luna 3u C18(2) 150x4.6 mm |
| Column Temperature | 20°C |
| Mobile Phase | 71:24:5 v./v. MeOH/H ₂ O/THF, with 5 mM ammonium formate |
| Gradient | Isocratic |
| Flow Rate | 1 mL/min |
| Injection Volume | 5-20 µL |
| UV wavelength | 228 nm |
| Polarity, scan type | Positive scan |
| Ionization Source | Electrospray Ionization (ESI) |
| Mass scan range | 300-400 Da |

Chromatograms

HPLC Chromatogram:



TIC Chromatogram:



Comparison of Impurity Profiles of Dronabinol

| RRT | m/z | M.W. | Generic Brand Capsule Made from AustinPharma API | Marinol® | Par Generic | Austin Pharma API Sample | Stressed API Sample Enriched with Impurities | Identification |
|------|-----|------|--|----------|-------------|--------------------------|--|-----------------------------|
| 0.23 | 329 | 328 | + | + | + | +, a | + | Hydroxydihydrocannabinol |
| 0.25 | 361 | 360 | + | + | + | + | + | Trihydroxydihydrocannabinol |
| 0.26 | 345 | 344 | + | + | + | - | + | Dihydroxydihydrocannabinol |
| 0.28 | 329 | 328 | +, a | +, a | +, a | - | +, a | Hydroxydihydrocannabinol |
| 0.30 | 329 | 328 | + | + | + | + | + | Hydroxydihydrocannabinol |
| 0.36 | 345 | 344 | + | + | + | - | +, a | Dihydroxydihydrocannabinol |
| 0.38 | 345 | 344 | + | + | + | + | + | Dihydroxydihydrocannabinol |
| 0.45 | 315 | 314 | - | - | - | - | - | Cannabidiol |
| 0.47 | 327 | 326 | - | + | + | + | + | Hydroxycannabinol |
| 0.63 | 313 | 312 | + | + | + | + | + | Dihydrocannabinol |
| 0.68 | 329 | 328 | + | + | + | - | - | Hydroxydihydrocannabinol |
| 0.71 | 313 | 312 | + | + | + | + | + | Dihydrocannabinol |
| 0.78 | 311 | 310 | + | + | b | + | + | Cannabinol |
| 0.82 | 313 | 312 | +, b | +, b | +, b | + | +, b | Dihydrocannabinol |
| 0.91 | 315 | 314 | + | + | + | + | + | Cis Δ^9 -THC |
| 1.00 | 315 | 314 | NA | NA | NA | NA | NA | Dronabinol, API |
| 1.06 | 313 | 312 | + | + | + | - | + | Dihydrocannabinol |
| 1.10 | 313 | 312 | + | + | + | +, a | + | Dihydrocannabinol |
| 1.15 | 315 | 314 | + | + | - | + | + | Δ^8 -THC |

+: Present in sample.

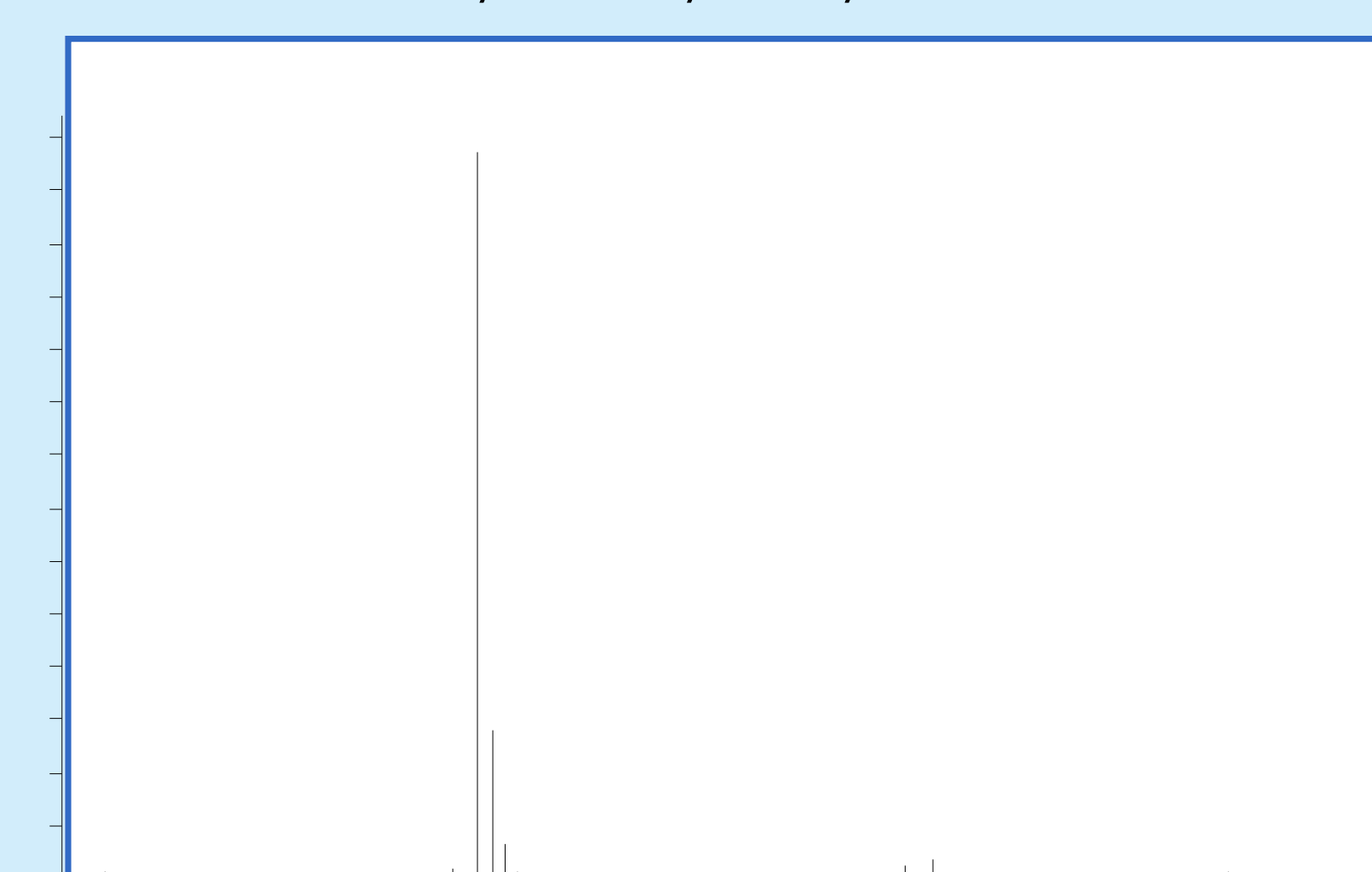
-: Not detected in sample or peak is too small to be extracted.

a: Mass spectrum is compromised because the impurity is low in the sample.

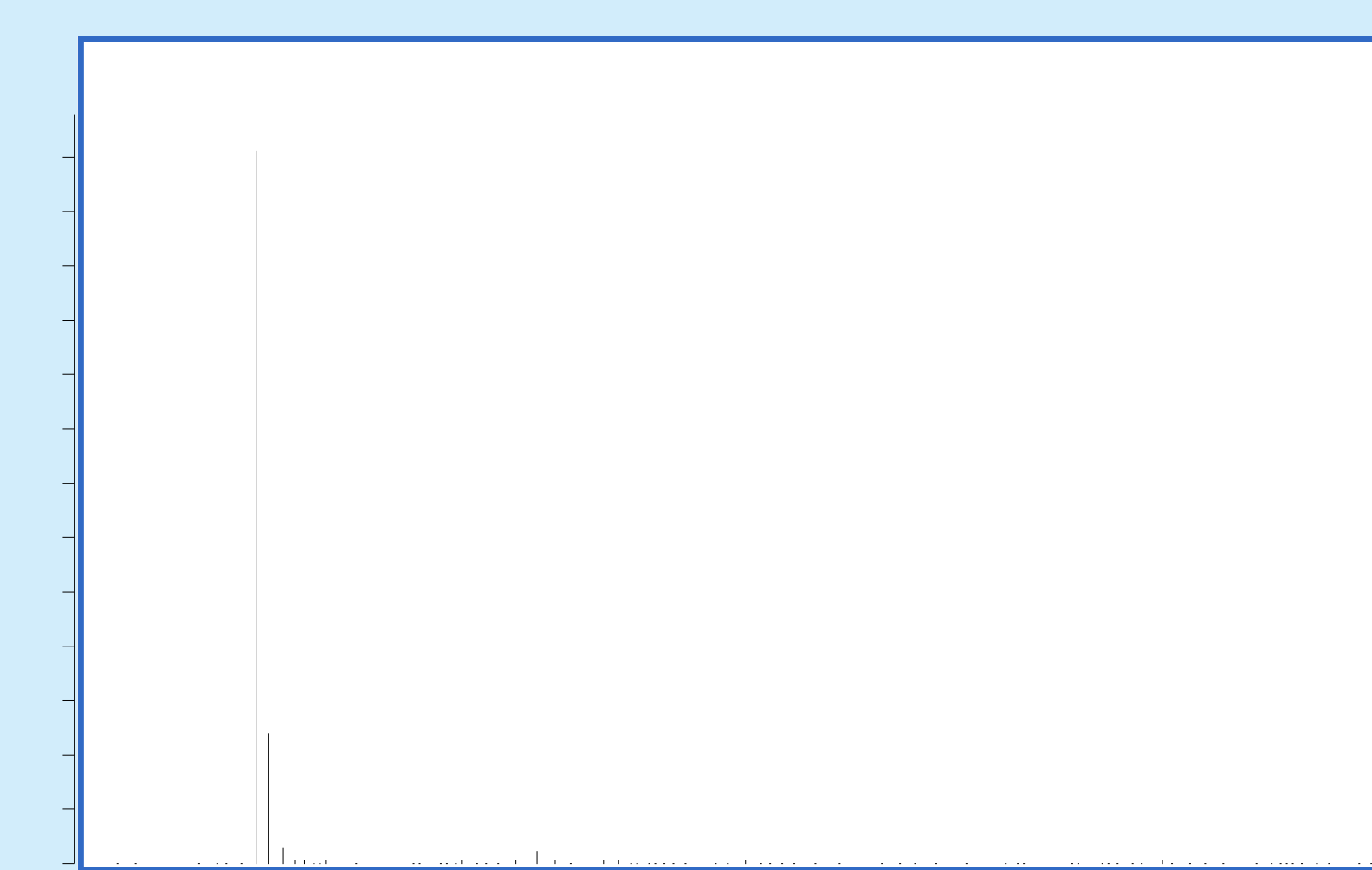
b: The mass spectra of RRT 0.82 for fresh API sample is 312. For the other four samples, it is a mixture of two components, with molecular weights 312 and 328. The ratio of the two peaks varies, but m/z 313 (M+H⁺) and m/z 329 (M+16+H⁺) are all evident. The m/z 329 peaks is oxygen adduct of m/z 313 peak. The structure of this impurity is proposed to be an isomer of Dihydrocannabinol and its oxygen adduct.

Mass Spectra of Selected Impurities

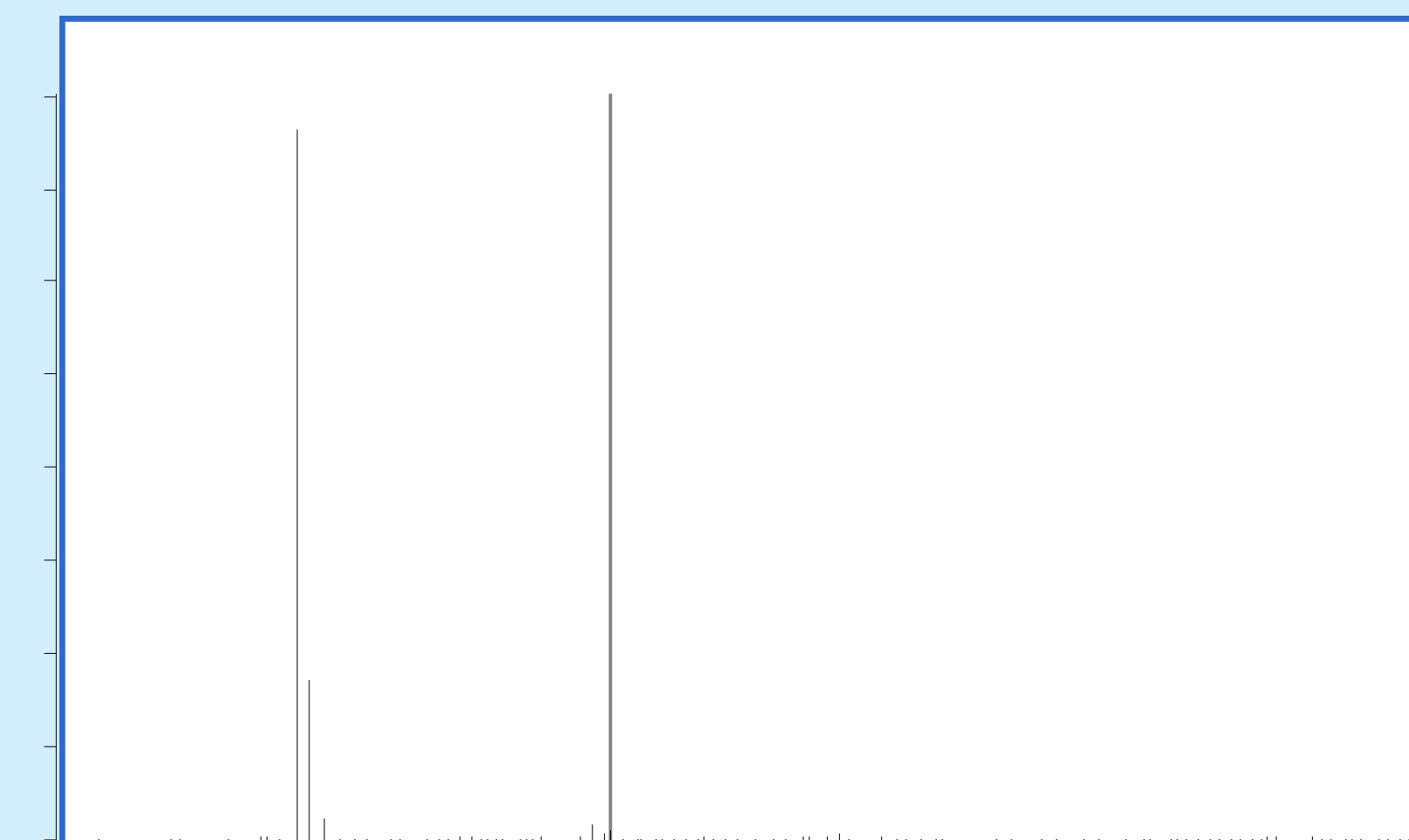
RRT 0.30 – Hydroxydihydrocannabinol



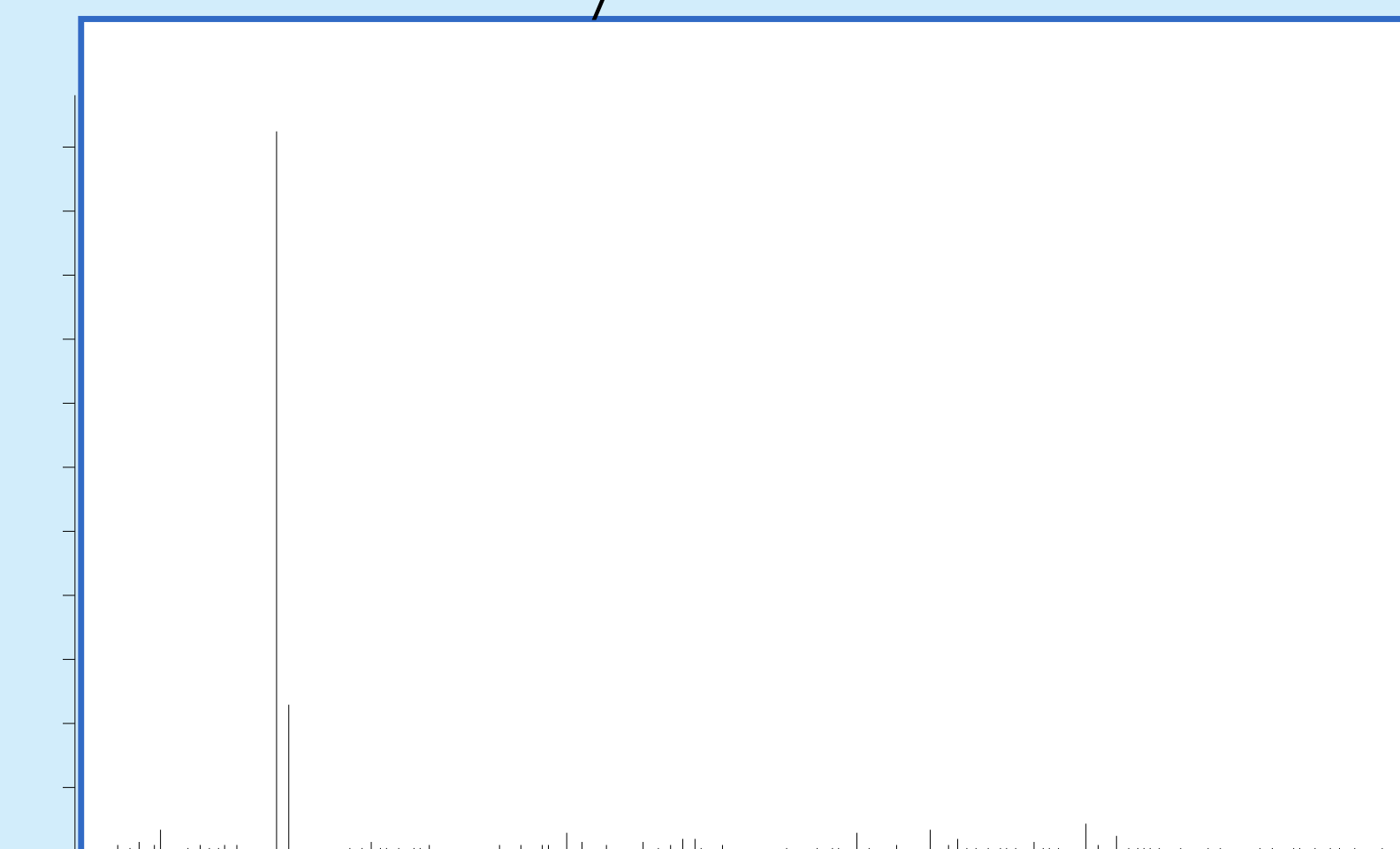
RRT 0.78 - Cannabinol



RRT 0.91 – Cis Δ^9 -THC

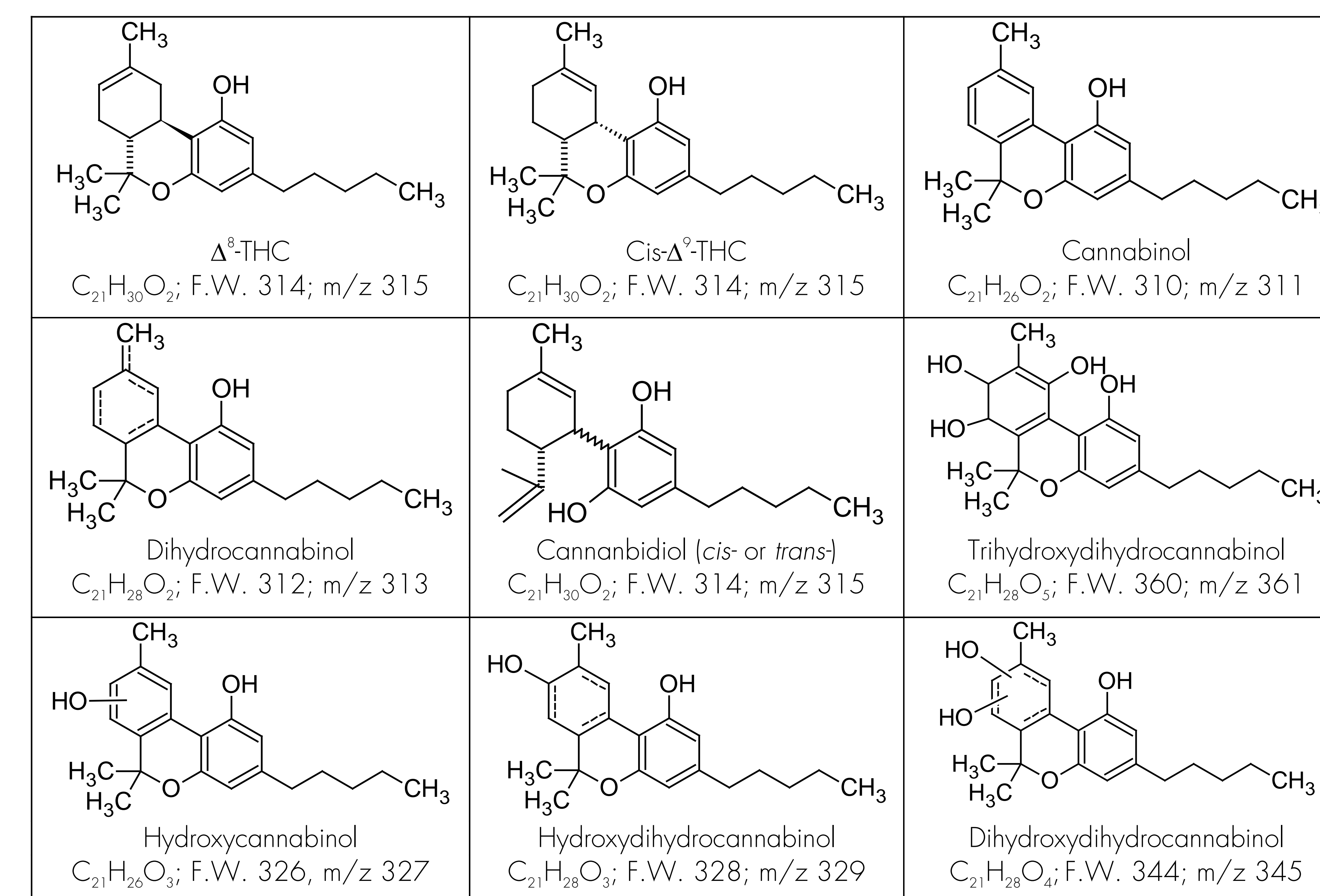


RRT 1.06 – Dihydrocannabinol



Structures of Dronabinol Impurities

- Identification of the specified impurities were confirmed by comparison to authentic references: RRT 0.78 – Cannabinol; RRT 0.91 – Cis Δ^9 -THC; RRT 1.15 – Δ^8 -THC.
- The proposed structures of other impurities were based on LCMS results. Extracted Ion Chromatogram (EIC) confirmed the relative retention time of these impurities. MRM studies did not provide additional information as the impurities are similar in structure.



Conclusions

- Impurities in Dronabinol Samples were identified.
- Specified impurities were Cannabinol, cis- Δ^9 -THC and Δ^8 -THC.
- Unspecified impurities were typically oxidative in nature. Structures were proposed for the observed unspecified impurities based on LCMS results.
- Similar impurity profiles were observed in all three capsules and stressed API, with an increase in number and amount of impurities.