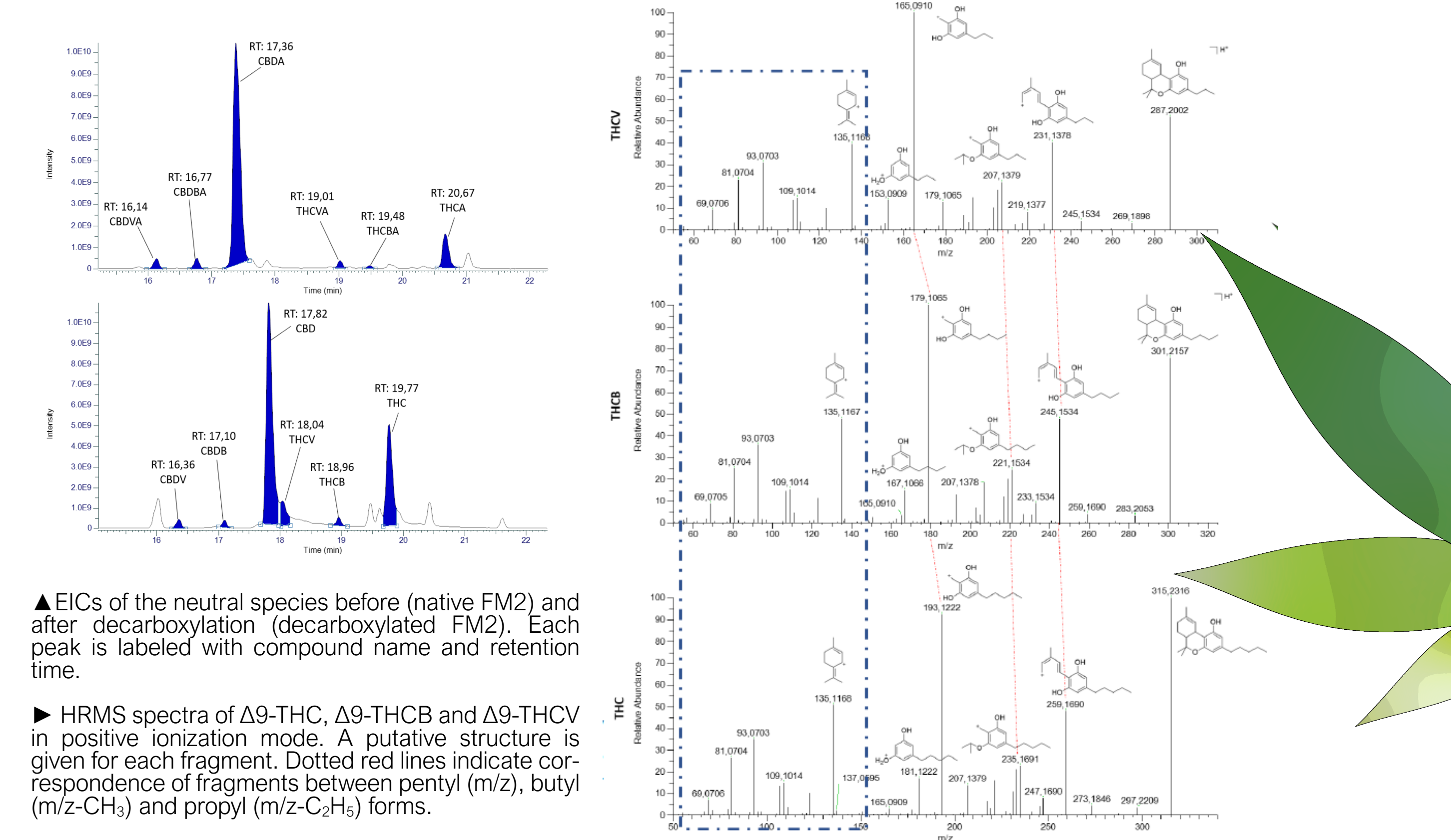
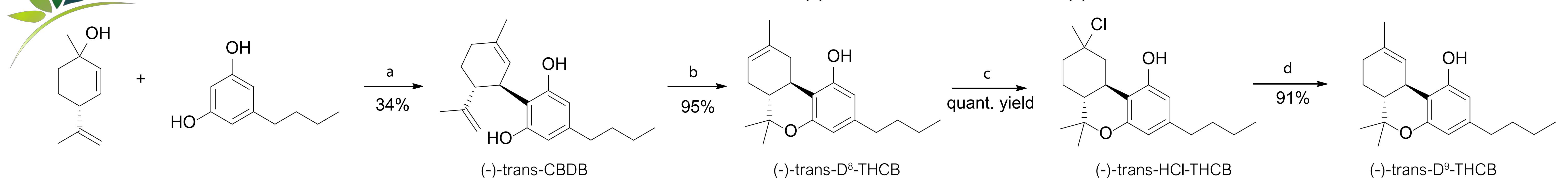


IDENTIFICATION OF (-)-TRANS-CBDB AND (-)-TRANS-Δ⁹-THCB BY UHPLC-HESI-ORBITRAP

The analysis of the decarboxylated FM2 ethanol extract showed beside the high amounts of CBD and THC and the well-known Cannabidivarin (CBDV) and Δ⁹-Tetrahydrocannabivarin (Δ⁹-THCV) the presence of two other phytocannabinoids that from MS/MS spectra analysis showed a structure CBD-like and THC-like, but differing from the CBD and THC for one methylene (CH₂) unit on the resorcinyl moiety.



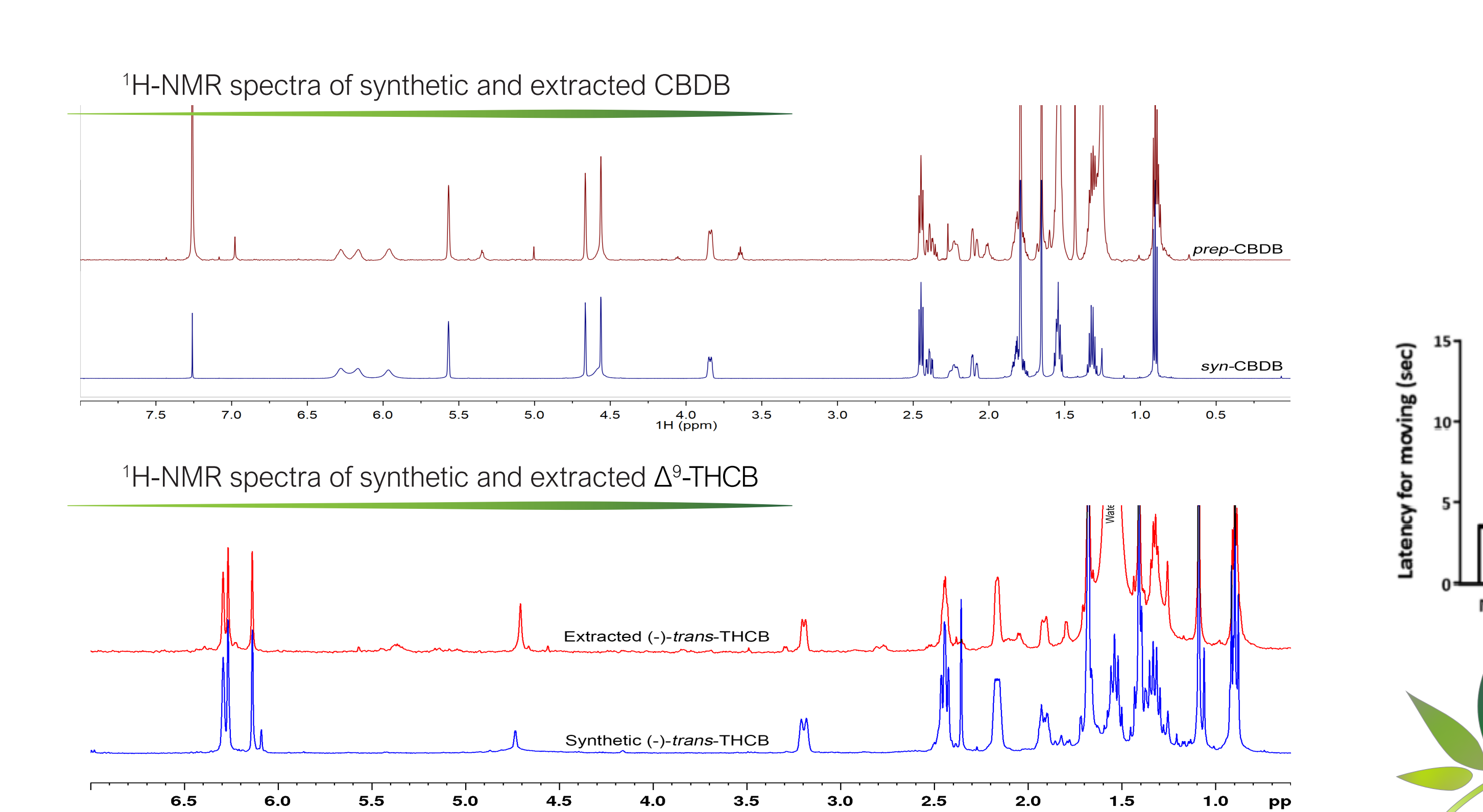
STEREOSELECTIVE SYNTHESIS OF THE ANALYTIC STANDARDS OF (-)-TRANS-CBDB AND (-)-TRANS-Δ⁹-THCB



Reagents and conditions: a) pTSA (cat.), DCM, 0 °C, 1h; a) pTSA (cat.), DCM, r.t, 48h; c) ZnCl₂ (0.5 eq.), 4N HCl in dioxane (1 mL per 100 mg of Δ⁸-THCB), dry DCM, argon, 0 °C to r.t., 2 h. d) 1.75M potassium amilate in toluene (2.5 eq.), dry toluene, argon, -15 °C, 2 h.

SPECTROSCOPIC CHARACTERIZATION

A full spectroscopic characterization (H-NMR, C-NMR, 2D-NMR, IR, CD, optical rotatory power) of the synthesized analytical standards and the purified cannabinoids from FM2 extract was performed. A near-perfect match of the two molecules was observed, thus confirming the chemical structure of the newly synthesized cannabinoid and in particular the Δ⁹ position of the double bond and the trans configuration of the dihydropyran ring.



REFERENCE

- Citt, C.; Linciano, P.; et al. Analysis of Impurities of Cannabidiol from Hemp. Isolation, Characterization and Synthesis of Cannabidibutol, the Novel Cannabidiol Butyl Analog. J. Pharm. Biomed. Anal. 2019, 175.
- Linciano, P.; Citt, C.; et al. Isolation of a High-Affinity Cannabinoid for the Human CB1 Receptor from a Medicinal Cannabis Sativa Variety: Δ⁹-Tetrahydrocannabutol, the Butyl Homologue of Δ⁹-Tetrahydrocannabinol. J. Nat. Prod. 2020, 83 (1), 88.

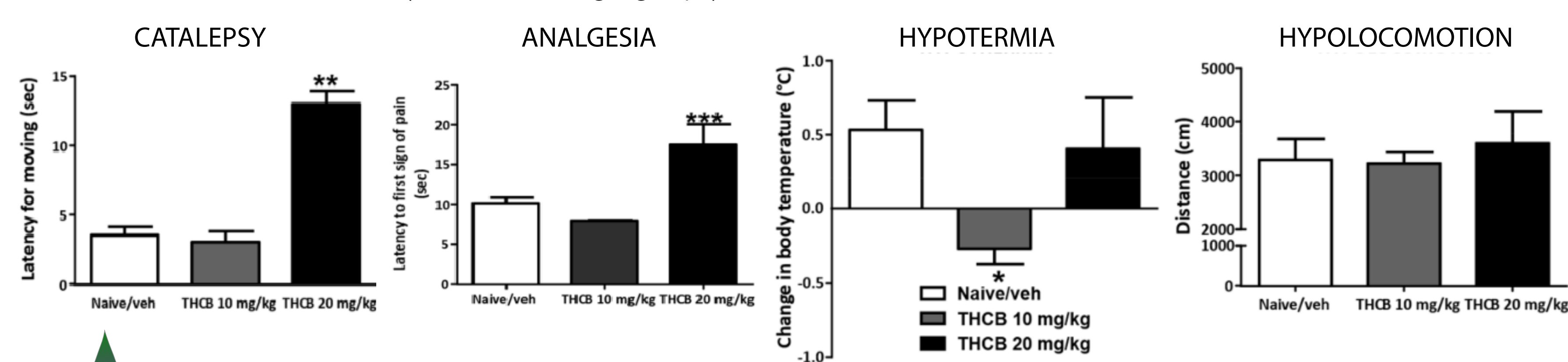
IN VITRO/IN VIVO CANNABIMIMETIC PROFILE OF Δ⁹-THCB

▼ Binding affinity (IC₅₀ and K_i) of (-)-trans-Δ⁹-THCB at human CB1 and CB2 receptors

	hCB1		hCB2	
	IC ₅₀ in nM	K _i in nM	IC ₅₀ in nM	K _i in nM
(-)-trans-Δ ⁹ -THCB	27.9	15	79	51
(-)-trans-Δ ⁹ -THC	-	40.7	-	36
(-)-trans-Δ ⁹ -THCV	-	75.4	-	62.8
CP 55940	1.7	0.93	-	-
WIN 55212-2	-	-	2.7	1.7

SD is within ± 10% of the value

▼ Effect of THCB (10 and 20 mg/kg, i.p.) in the tetrad test.



CONCLUSION

- The butyl homologues of CBD (CBDB) and Δ⁹-THC (Δ⁹-THCB) were isolated from a medicinal C. sativa.
- The authentic standards obtained via stereoselective synthesis.
- The binding affinity of Δ⁹- THCB for hCB1 is similar to that of Δ⁹-THC and higher than that of Δ⁹-THCV.
- Δ⁹-THCB showed analgesic effects in the formalin test in mice.
- The results of the tetrad test indicated that Δ⁹-THCB should be a partial agonist for the CB1 receptor.
- Δ⁹-THCB and CBDB might represent two new phytocannabinoids on which to focus in the near future, in order to further investigate the complex cannabinoid pharmacological effects