

Isolation and pharmacological evaluation of Δ^9 -tetrahydrocannabiphorol, the new heptyl homologue of Δ^9 -tetrahydrocannabinol: new insights on cannabis research



Cinzia Citti,^{a,b,c} Pasquale Linciano,^c Fabiana Russo,^c Livio Luongo,^d Monica Iannotta,^d Sabatino Maione,^d Aldo Laganà,^{b,e} Anna Laura Capriotti,^e Flavio Forni,^c Maria Angela Vandelli,^c Giuseppe Gigli,^b and Giuseppe Cannazza,^{b,c,*}

^a Meditekology (CNR spin-off company), Via Arnesano, 73100 Lecce, Italy

^b CNR NANOTEC, Istituto di Nanotecnologia, Via Monteroni, 73100 Lecce, Italy

^c Department of Life Sciences, University of Modena and Reggio Emilia, Via G. Campi 103, 41125 Modena, Italy

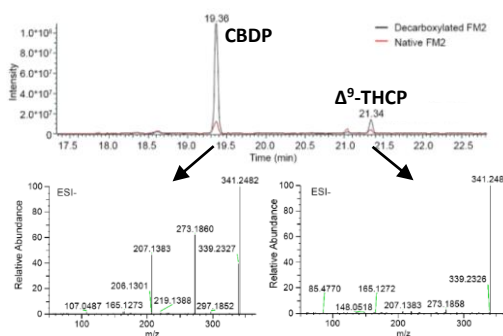
^d Department of Experimental Medicine, Division of Pharmacology, Università della Campania "L. Vanvitelli", Via Santa Maria di Costantinopoli 16, 80138 Naples, Italy

^e Department of Chemistry, Sapienza University of Rome, Piazzale Aldo Moro 5, 00185 Rome, Italy

cinzia.citti@unimore.it

The wide structural variety of phytocannabinoids in *Cannabis sativa* L. derives from the combination of a terpene and a resorcinyl moiety with an alkyl side chain.^[1] A longer side chain leads to cannabimimetic properties far higher than those of the well-known Δ^9 -tetrahydrocannabinol (Δ^9 -THC).^[2] To date, no phytocannabinoid with a linear side chain longer than five carbon units has been reported.

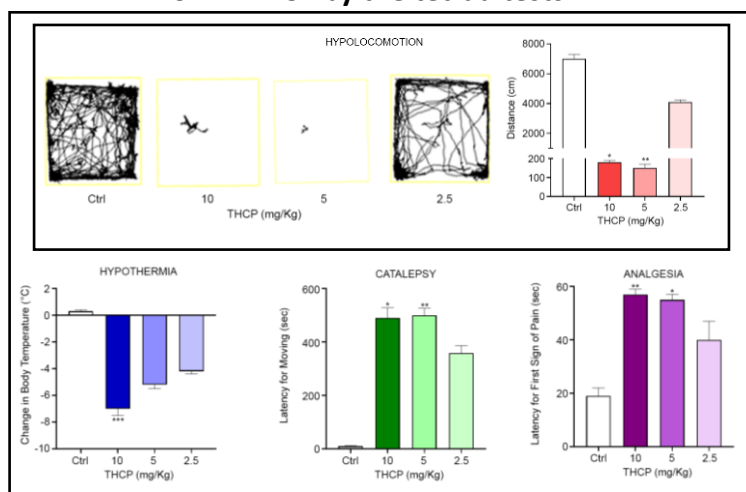
1. Identification of CBDP and Δ^9 -THCP by UHPLC-HRMS



2. Isolation and full characterization of CBDP and Δ^9 -THCP (NMR, CD, $[\alpha]_D^{20}$) of CBDP and Δ^9 -THCP by semi-prep liquid chromatography

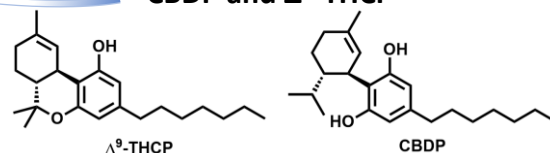
For the first time Δ^9 -tetrahydrocannabiphorol (Δ^9 -THCP) and cannabidiphorol (CBDP), the heptyl homologues of Δ^9 -THC and cannabidiol (CBD) respectively, were identified in the Italian medicinal cannabis variety FM2 by *ultrahigh performance liquid chromatography coupled to high-resolution mass spectrometry (UHPLC-HRMS)*.

5. *In vivo* determination of the cannabinoid profile of Δ^9 -THCP by the tetrad tests



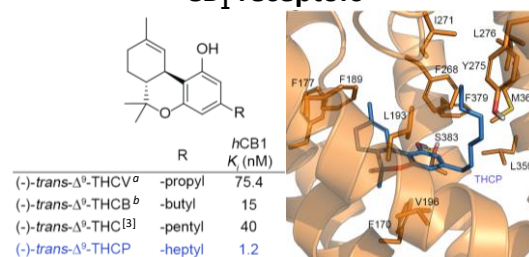
Δ^9 -THCP reduced locomotion and rectal temperature and induced catalepsy and analgesia suggesting a *THC-like cannabimimetic activity*

3. Stereoselective synthesis of CBDP and Δ^9 -THCP



The stereochemistry of Δ^9 -THCP and CBDP was assigned by comparison of the physicochemical properties of isolated and synthetic compounds.

4. *In vitro* binding affinity at human CB₁ receptors



^a THCV (Tetrahydrocannabivarin)^[3], ^b THCB (Tetrahydrocannabutol)^[3]

The binding affinity of Δ^9 -THCP resulted over 30-fold higher than that of Δ^9 -THC

References

- Hanuš, L. O., *et al.* Phytocannabinoids: a unified critical inventory. *Nat. Prod. Rep.* **2016**, *33*, 1357-1392.
- Martin, B. R. *et al.* Manipulation of the Tetrahydrocannabinol Side Chain Delineates Agonists, Partial Agonists, and Antagonists. *J. Pharmacol. Exp. Ther.* **1999**, *290*, 1065-1079.
- Linciano, P. *et al.* Isolation of a high affinity cannabinoid for human CB₁ receptor from a medicinal cannabis variety: Δ^9 -Tetrahydrocannabutol, the butyl homologue of Δ^9 -tetrahydrocannabinol. *Nat. Prod.* **2020**, *83*, 1, 88-98.