

**The cannabidiol enigma:
are the metabolites of CBD pharmacologically active?**

István Ujváry

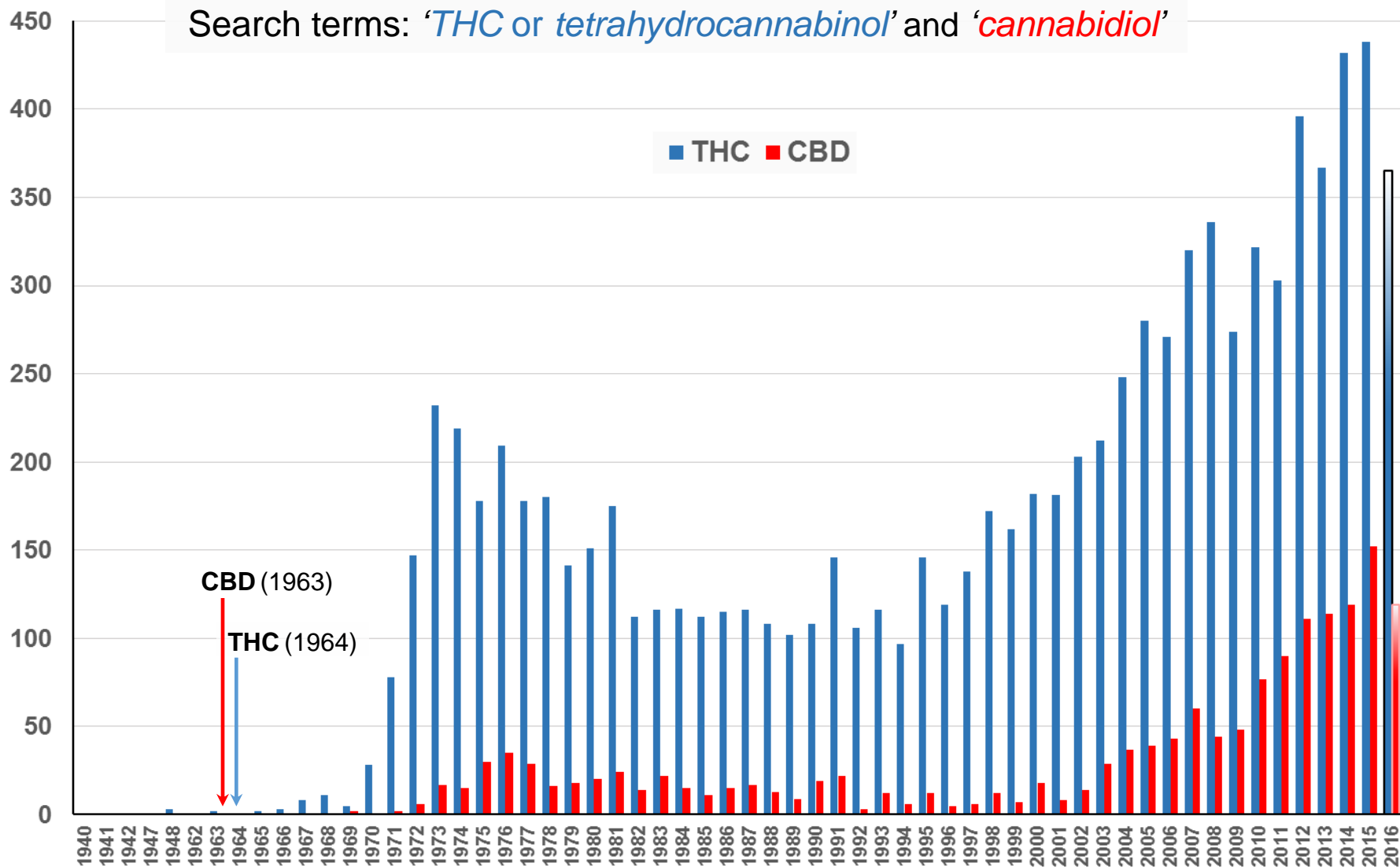
*i*Kem BT

Budapest, Hungary

Cann10 - The International Medical Cannabis Conference 2016
12-13 September, 2016, Tel Aviv

In terms of publications, research on CBD lags behind THC

as reflected by the number of citations in *PubMed* database



Cannabidiol monotherapy typically requires large doses

In humans, reported daily oral therapeutic CBD dose range: 15–800 mg

Reasons:

pharmacodynamics: low efficacy

pharmacokinetics: poor bioavailability



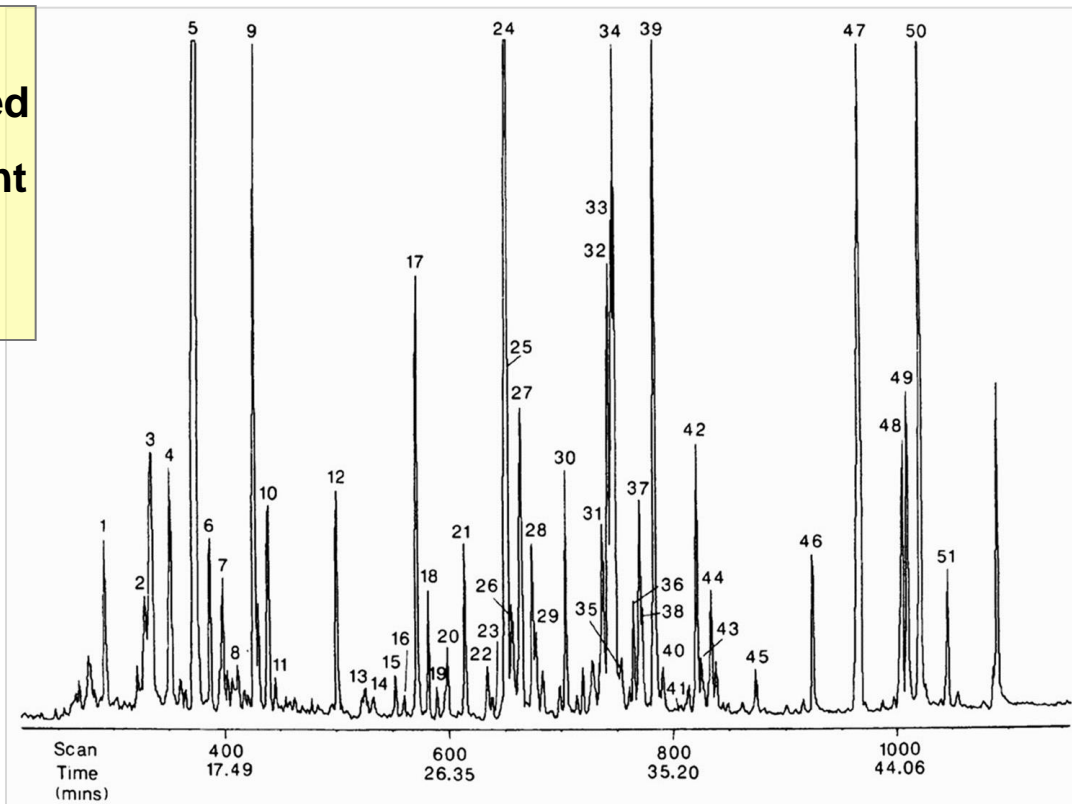
Metabolites of cannabidiol identified in human urine

D. J. HARVEY† and R. MECHOULAM‡

† University Department of Pharmacology, South Parks Road,
Oxford OX1 3QT, UK

‡ Faculty of Medicine, The Hebrew University of Jerusalem,
Jerusalem 91 120 Israel

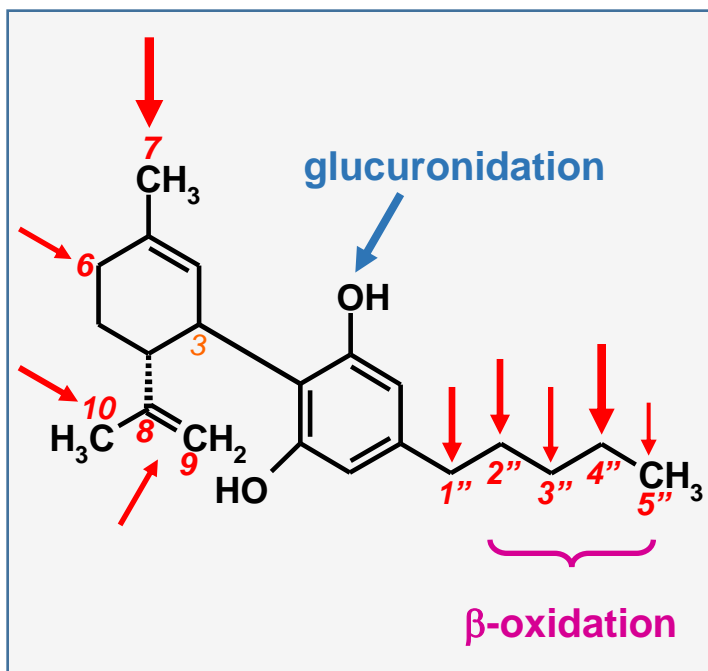
33 metabolites identified
4 metabolites partly characterized
from the urine of a dystonic patient
treated chronically with
600 mg CBD daily



Cannabidiol is extensively oxidized at multiple sites

over 35 oxidative human metabolites have been detected¹

+5 other oxidative derivatives produced *in vitro* by recombinant human CYP450 isoforms²



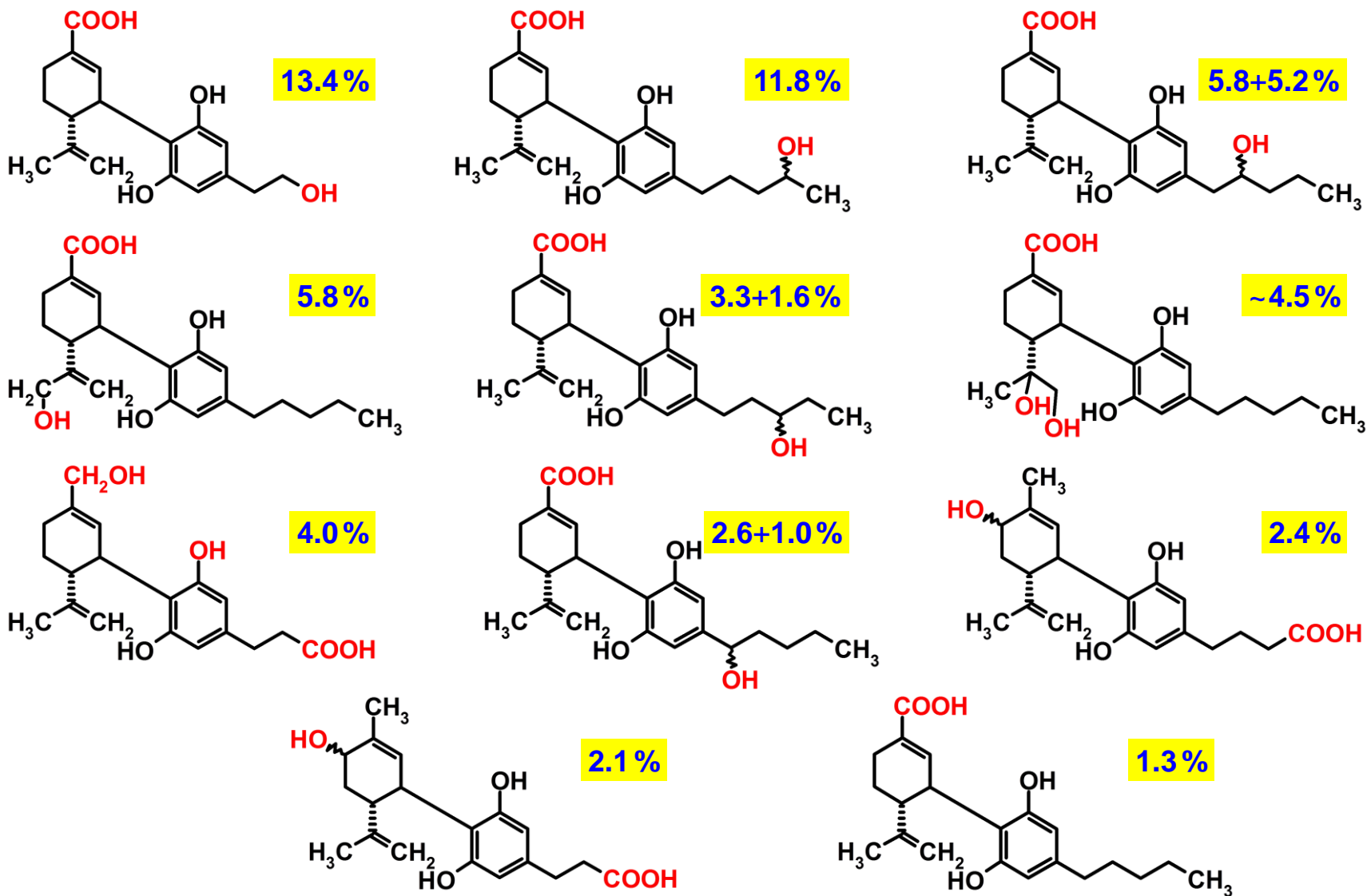
Cytochrome P450-enzymes catalyzing the hydroxylation of CBD		
CYP450 isoform	Target C-atom	
	Experimental ²	Predicted ³ (<i>not found by expt.</i>)
1A1	C6, C7, C1''	–
1A2	C6, C1''–C4''	C6, C7, C8=9, C10, C3'', C4'', C5''
2C9	C6, C7, C4'', C5''	C6, C7, C3, C8=9, C10, C4'', C5''
2C19	C6, C7, C4''	C6, C7, C8=9, C10, C1'', C3'', C4'', C5''
2D6	C6, C7, C4'', C5''	C6, C7, C8=9, C10, C1'', C3'', C4'', C5''
3A4	C6, C7, C2'', C4'', C5''	C4, C6, C7, C8=9, C3'', C4'', C5''
3A5	C6, C7, C2'', C3'', C4''	–

¹Harvey & Mechoulam (1990) *Xenobiotica* **20**, 303; ²Jiang et al (2011) *Life Sci* **89**, 165

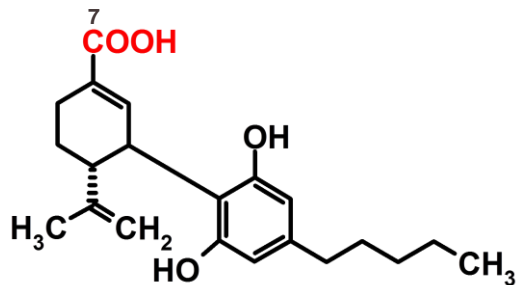
³CYP450 regioselectivity calculated with  StarDrop 6.3 www.optibrium.com/stardrop

Most abundant **oxidative** urinary CBD metabolites in a chronic user

alcohols & carboxylic acids include side chain degradants

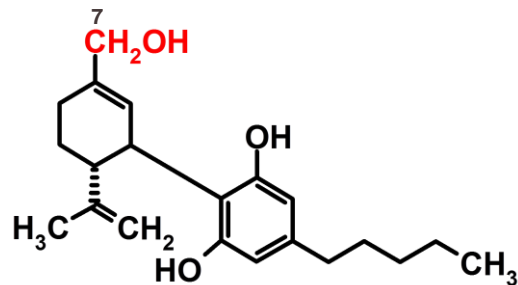


Bioactivity data are on CBD metabolites are scarce
only for 4 single-site oxidative products



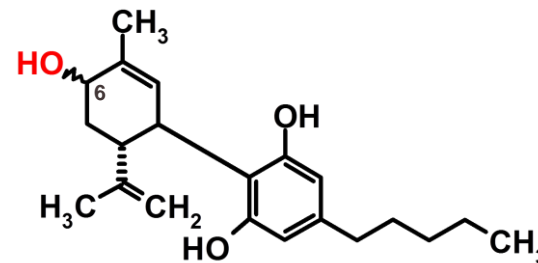
7-COOH-CBD

1.34%



7-OH-CBD

0.64%



6 α / β -OH-CBD

0.07%

relative amount of urinary cannabinoids as determined by Harvey & Mechoulam (1990)

Effects of CBD metabolites on the endocannabinoid system *in vitro*

CBD metabolite	Assay <i>in vitro</i>	Activity, μM
7-OH-CBD	<i>CB1/CB2 receptor</i>	$K_i > 10$
7-COOH-CBD	<i>CB1/CB2 receptor</i>	$K_i > 10$
7-OH-CBD	<i>FAAH inhibition</i>	$\text{IC}_{50} = 34$
7-COOH-CBD	<i>FAAH inhibition</i>	$\text{IC}_{50} > 100$
7-OH-CBD	<i>Anandamide uptake inhibition</i>	$\text{IC}_{50} \sim 50$
7-COOH-CBD	<i>Anandamide uptake inhibition</i>	$\text{IC}_{50} > 50$

Biological activities of CBD metabolites in animals

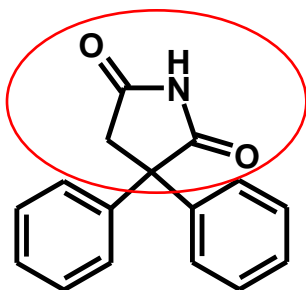
CBD metabolite	Effect, animal, route of administration	Dose	Degree of activity
7-OH-CBD 7-COOH-CBD	<i>antinociceptive, mouse, ip</i> <i>antinociceptive, mouse, ip</i>	20 mg/kg 20 mg/kg	each fully blocked formalin-induced pain-related behaviour
7-OH-CBD 7-COOH-CBD	<i>antiinflammatory, mouse, ip</i> <i>antiinflammatory, mouse, ip</i>	40 mg/kg 40 mg/kg	< 20 mg/kg indomethacin ≤ 20 mg/kg indomethacin

Anxiolytic & anticonvulsant effects also observed.

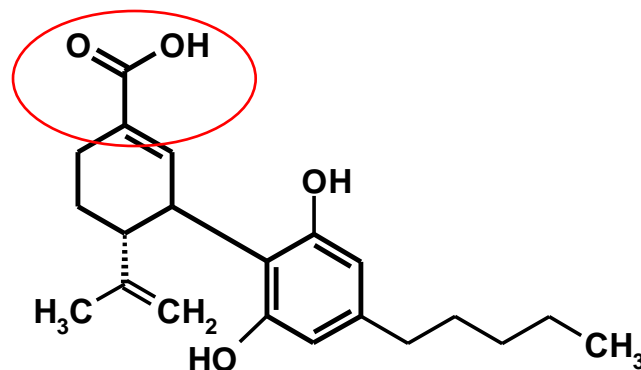
Biological activity of CBD metabolites in humans

Not known

Similarity of 7-COOH-CBD and the anticonvulsant phenytoin *structural (and pharmacological?)*

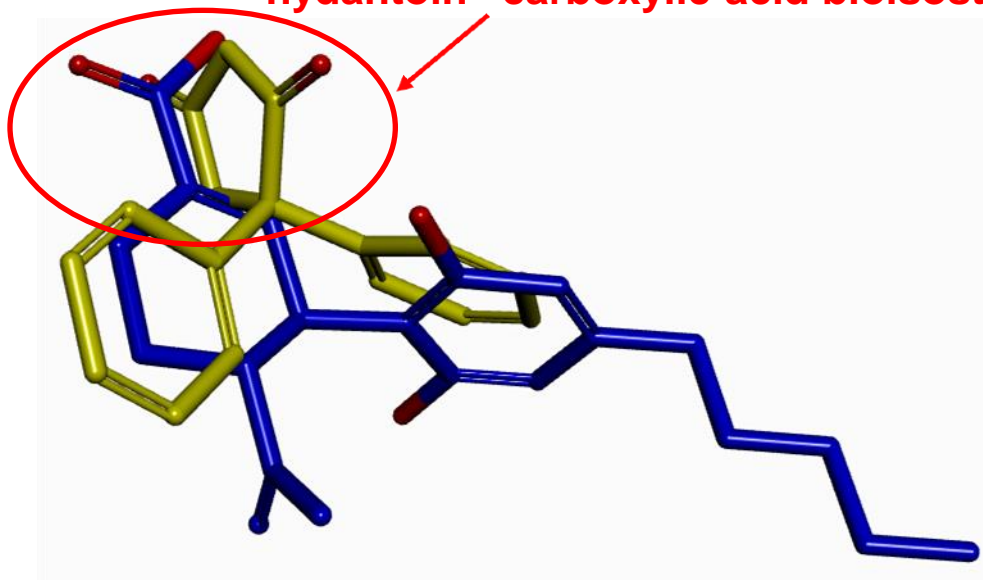


phenytoin



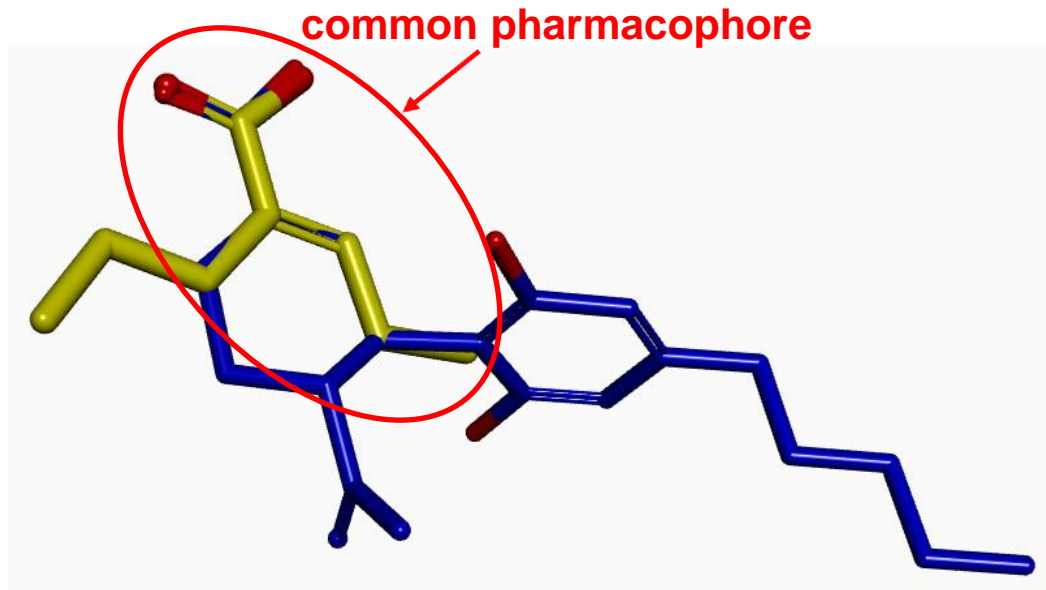
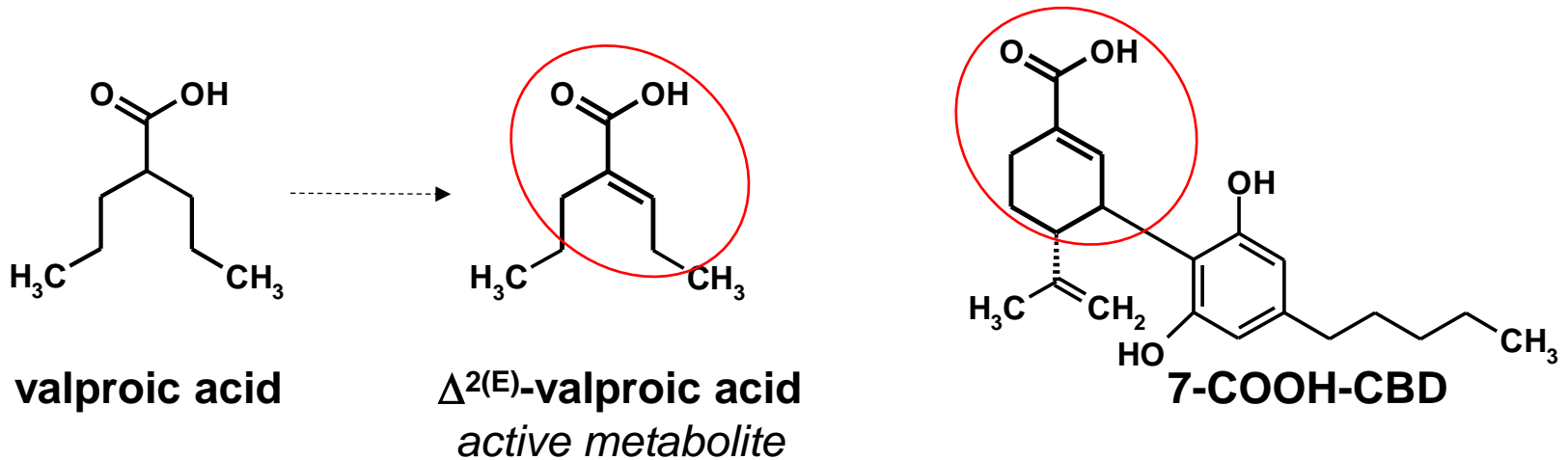
7-COOH-CBD

hydantoin-carboxylic acid bioisosterism



Based on: Tamir, Mechoulam & Meyer (1990) *J Med Chem* **23**, 220
Molecular modeling by *Discovery Studio Visualizer 4.1* (Accelrys Inc.)

Similarity of 7-COOH-CBD and the anticonvulsant $\Delta^{2(E)}$ -valproate *structural (and pharmacological?)*



On valproic acid analogues, see: Bialer *et al* (1994) *Pharm World Sci* **16**, 2
Molecular modeling by *Discovery Studio Visualizer 4.1* (Accelrys Inc.)

SUMMARY

Investigation of CBD metabolites is needed

- ✦ **identify bioactivity of main metabolites** (pharmacological profiling)
- ✦ **study the involvement of metabolites in CBD's action *in vivo***
- ✦ **explore further therapeutic potential of CBD metabolites**
- ✦ **use single metabolite in therapy** (proprietary reasons)