

**Cannabinoid metabolites as inhibitors of major hepatic CYP450 enzymes, with implications for cannabis-drug interactions**

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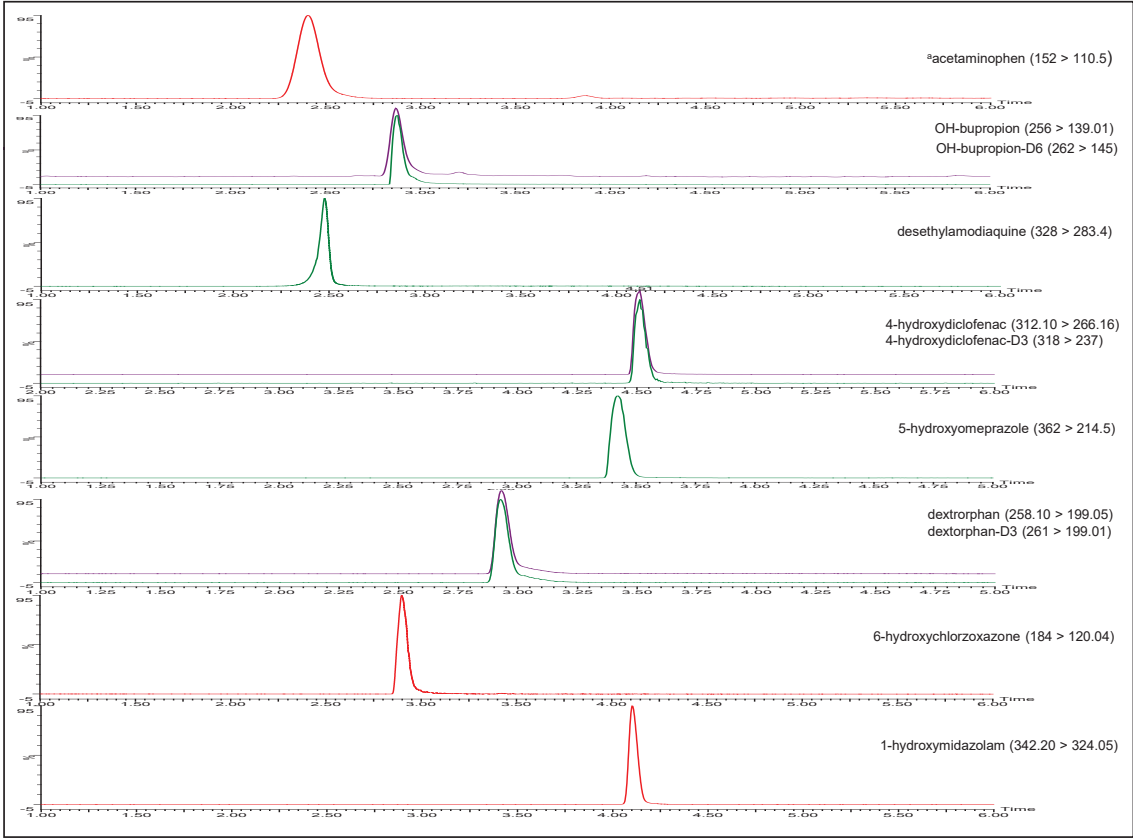
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## Supplemental Figure Legends

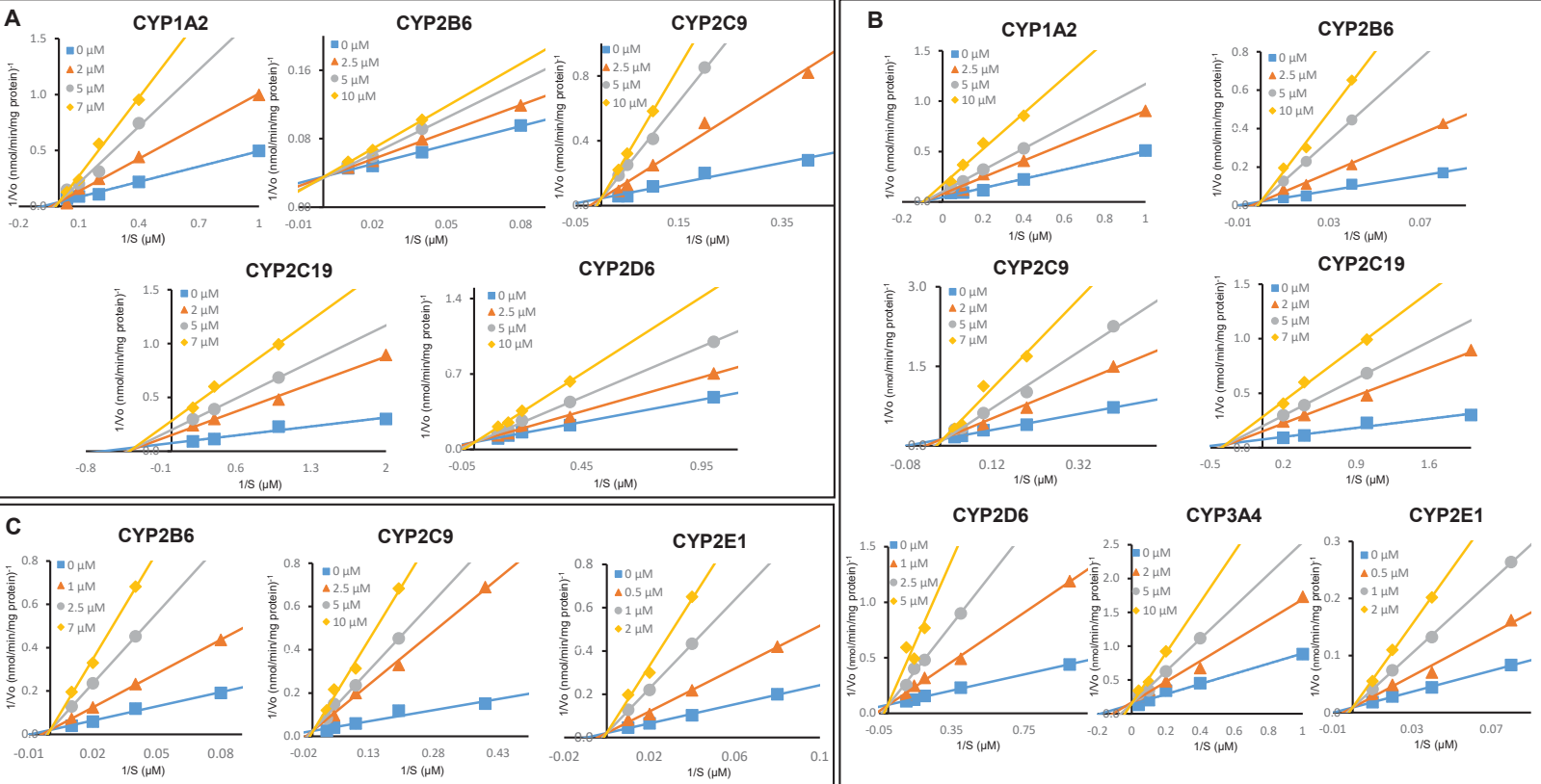
**Supplemental Figure 1. Chromatograms of probe metabolites in assays containing microsomes from CYP450-overexpressing cells.** The probe metabolite examined is described with the mass transition shown in brackets. The traces for D3- or D6-labeled OH-bupropion, 4-hydroxydiclofinac, and dextrorphan are shown in red.

**Supplementary Figure 2. Lineweaver-Burk plots for the inhibition of CYP450 activity in microsomes from recombinant CYP450-overexpressing cells by cannabinoids. A,** inhibition by THC; **B,** inhibition by CBD; **C,** inhibition by CBN.

Supplemental Figure 1



### Supplemental Figure 2



**Supplemental Table 1.** Conditions used for inhibition assays.

CYP	probe substrate	metabolite	probe inhibitor	[substrate] ( $\mu\text{M}$ )	incubation time (min)
CYP1A2	phenacetin	acetaminophen	furafylline	10	15
CYP2B6	bupropion	hydroxybupropion	clopidogrel	100	15
	efavirenz	8-hydroxyefavirenz		8	15
CYP2C8	amodiaquine	desethylamodiaquine	montelukast	2	15
CYP2C9	diclofenac	4'-hydroxydiclofenac	sulfaphenazole	10	15
	S-warfarin	7-hydroxywarfarin		10	15
CYP2C19	omeprazole	5-hydroxyomeprazole	tranylcypromine	1.0	30
CYP2D6	dextromethorphan	dextrorphan	quinidine	5	15
	bufuralol	1-hydroxybufuralol		10	20
CYP2E1	chlorzoxazone	6 hydroxychlorzoxazone	chlormethiazole	100	15
CYP3A4	midazolam	1-hydroxymidazolam	ketoconazole	5	8

**Supplemental Table 2.** Inhibition of cannabinoids and THC metabolites against additional probe substrates for CYP2B6, CYP2D6, and CYP2C9 using microsomes from recombinant CYP450-overexpressing cells.

probe substrate	microsoma l protein	THC		11-OH-THC		THC-COO-Gluc		CBD		CBN	
		IC <sub>50</sub>	IC <sub>50,μ</sub>	IC <sub>50</sub>	IC <sub>50,μ</sub>	IC <sub>50</sub>	IC <sub>50,μ</sub>	IC <sub>50</sub>	IC <sub>50,μ</sub>	IC <sub>50</sub>	IC <sub>50,μ</sub>
efavirenz	rCYP2B6	2.8 ± 0.81	0.14 ± 0.0405	5.1 ± 0.52	0.255 ± 0.026	3.2 ± .92	0.16 ± 0.046	3.2 ± 0.58	0.384 ± 0.070	2.8 ± 0.12	0.14 ± 0.0060
bufuralol	rCYP2D6	5.2 ± 0.85	0.26 ± 0.0425	3.1 ± 0.53	0.155 ± 0.026	7.0 ± 1.1	0.35 ± 0.055	1.5 ± 0.28	0.18 ± 0.034		NA <sup>a</sup>
S-warfarin	rCYP2C9	3.1 ± 0.48	0.15 ± 0.024	2.8 ± .35	0.14 ± 0.018	7.2 ± .42	0.36 ± 0.021	1.8 ± .21	0.216 ± 0.025	1.4 ± 0.20	0.07 ± 0.010

<sup>a</sup> NA, not analyzed.