

Article Title: Cytochrome P450-mediated oxidative metabolism of abused synthetic cannabinoids found in “K2/Spice”: Identification of novel cannabinoid receptor ligands

Authors: Krishna C. Chimalakonda, Kathryn A. Seely, Stacie M. Bratton, Lisa K. Brents, Cindy L. Moran, Gregory W. Endres, Laura P. James, Paul F. Hollenberg, Paul L. Prather, Anna Radomska-Pandya, Jeffery H. Moran

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Supplemental Table 1. MS/MS Experimental Conditions for Specific Reaction Monitoring

	Analyte	Q1 (m/z)	Q3 (m/z)	CE ^a (V)	EP ^b (V)	DP ^c (V)	CXP ^d (V)
SRM	1, 3-7, and 9	358	155	37	10	86	12
	8	372	155	37	10	86	12
	2	360	155	37	10	86	12
	10	376	155	37	10	86	12
IDA-EPI	1–10	[MH] ⁺	80–600	40	10	40	NA

^aCE, Collision Energy; ^bEP, Entrance Potential; ^cDP, Declustering Potential; ^dCXP, Collision

Cell Exit Potential, NA, Not applicable

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Supplemental Table 2. Kinetic parameters for JWH-018 oxidation. “ K_m ” and “ V_{max} ” values are given in μM and pmole/min/nmole protein for recombinant P450 isoforms and pmole/min/mg protein for HLM, respectively.

JWH-018 Metabolites		JWH-018 5-OH	JWH-018 6-OH	JWH-018 7-OH	JWH-018 Unidentified-OH
CYP1A2	V_{max}	ND	2696 ± 72	ND	436 ± 16
	K_m	ND	7.2 ± 0.87	ND	5.0 ± 0.83
	Kinetic Fit	ND	M-M	ND	M-M
CYP2C9	V_{max}	60 ± 2.2	207 ± 6	ND	ND
	K_m	2.3 ± 0.31	2.5 ± 0.27	ND	ND
	Kinetic Fit	Hill, n= 1.6	Hill, n= 1.3	ND	ND
CYP2C19	V_{max}	ND	5035	ND	431
	K_m	ND	297	ND	85
	Kinetic Fit	ND	*	ND	*
CYP2D6	V_{max}	13 ± 0.56	16.6 ± 0.82	2.6 ± 0.17	ND
	K_m	0.59 ± 0.16	2.9 ± 0.7	3.0 ± 0.98	ND
	Kinetic Fit	M-M	M-M	M-M	ND
HLM	V_{max}	2.6 ± 0.15	3.2 ± 0.18	ND	4.5 ± 0.6
	K_m	5.0 ± 0.82	3.2 ± 0.58	ND	25.4 ± 9.0
	Kinetic Fit	Hill, n= 2.3	Hill, n= 2.7	ND	M-M

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Supplemental Table 3. Kinetic parameters for AM2201 oxidation. “K_m” and “V_{max}” values are given in μM and pmole/min/nmole protein for recombinant P450 isoforms and pmole/min/mg protein for HLM, respectively

AM2201 Metabolites		AM2201 Unidentified-1 OH	AM2201 Unidentified-2 OH
CYP1A2	V _{max}	906 ± 40	ND
	K _m	7.3 ± 1.3	ND
	Kinetic Fit	M-M	ND
CYP2C9	V _{max}	128 ± 8.3	ND
	K _m	1.5 ± 0.97	ND
	Kinetic Fit	M-M	ND
CYP2C19	V _{max}	732 ± 30	ND
	K _m	4.2 ± 0.8	ND
	Kinetic Fit	M-M	ND
CYP2D6	V _{max}	131 ± 3.4	11.6 ± 0.6
	K _m	3.0 ± 0.4	1.8 ± 0.6
	Kinetic Fit	M-M	M-M
HLM	V _{max}	26	ND
	K _m	255	ND
	Kinetic Fit	Hill, n = 0.69 [#]	ND

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Supplemental Table 4. Fractional contribution ($f_{m, CYP}$) of recombinant human P450 (rCYP) isoforms during JWH-018 oxidation. Intrinsic clearance (CL_{int}) values are given in $\mu\text{L}/\text{min}/\text{nmole}$ P450 and hepatic abundance values of specific P450s (Proctor et al., 2004; Rowland-Yeo et al., 2003) are given in nmoles/mg protein, respectively.

JWH-018 Metabolites		CL_{int} in rCYP	Hepatic Abundance	Fractional Contribution of each P450 ($f_{m, CYP}$)
CYP1A2	5-OH	0	0.045-0.052	0
	6-OH	374		0.75-0.85
	7- OH	0		0
	Unidentified-OH	87.2		0.98-0.99
CYP2C9	5-OH	26.1	0.032-0.073	0.81-0.92
	6-OH	83		0.14-0.24
	7- OH	0		0
	Unidentified-OH	0		0
CYP2C19	5-OH	0	0.006-0.014	0
	6-OH	17		0.013
	7- OH	0		0
	Unidentified-OH	5.1		0.024
CYP2D6	5-OH	22	0.009-0.01	0.081
	6-OH	5.7		0.002
	7-OH	0.870		1
	Unidentified-OH	0		0

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Supplemental Table 5. Fractional contribution ($f_{m, CYP}$) of recombinant human P450 (rCYP) isoforms during AM2201 oxidation. Intrinsic clearance (CL_{int}) values are given in $\mu\text{L}/\text{min}/\text{nmole}$ P450 and hepatic abundance values of specific P450s (Proctor et al., 2004; Rowland-Yeo et al., 2003) are given in nmoles/mg protein, respectively.

AM2201 metabolites		CL_{int} in rCYP	Hepatic Abundance	Fractional Contribution of each P450 ($f_{m, CYP}$)
CYP1A2	Unidentified-OH-1	124		0.42-0.56
	Unidentified-OH-2	0	0.045-0.052	0
CYP2C9	Unidentified-OH-1	85		0.29-0.40
	Unidentified-OH-2	0	0.032-0.073	0
CYP2C19	Unidentified-OH-1	174		0.19
	Unidentified-OH-2	0	0.006-0.014	0
CYP2D6	Unidentified-OH-1	44		0.025
	Unidentified-OH-2	6.4	0.009-0.01	1