Human phase-I metabolism of three synthetic cannabinoids bearing a cumyl moiety and a cyclobutyl methyl or norbornyl methyl tail: Cumyl-CBMEGACLONE, Cumyl-NBMEGACLONE and Cumyl-NBMINACA

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Figure S8. Spectra of metabolites of Cumyl-NBMEGACLONE, as obtained from the analysis of pHLM (by auto-MS/MS for M7, M11-23 or bbCID). Metabolites only generated in vitro are shown grouped together. *m/z* is shown as theoretical, colored and in italic, and experimental, bolded in black, just below.

Figure S9. Extracted-ion chromatogram (XIC) of one authentic urine sample containing Cumyl-NBMINACA metabolites. Mass tolerance: 0.002 Da for all.

Figure S10. Extracted-ion chromatogram (XIC) of one pHLM assay containing in vitro generated Cumyl-NBMINACA metabolites. Mass tolerance: 0.002 Da for all.

Figure S11. Spectra of metabolites of Cumyl-NBMINACA, as obtained from the analysis of urine samples and compared to pHLM (by bbCID). Metabolites only generated in vitro are shown grouped together. *m/z* is shown as theoretical, colored and in italic, and experimental, bolded in black, just below.

Figure S1: ^{1}H-NMR (500 MHz, 297 K, acetone-d_6) data of the synthesised Cumyl-NBMEGACLONE (purity >95%).

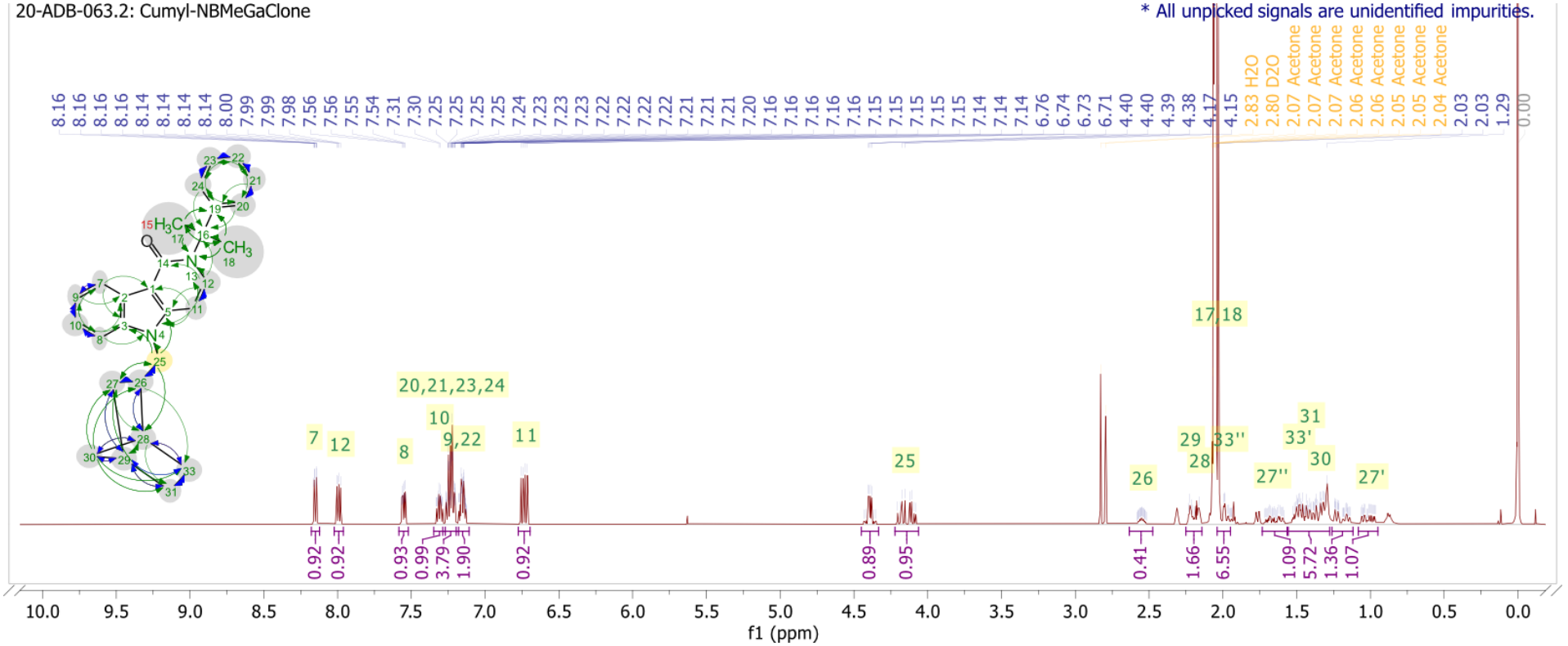

Table S1: Chemical shifts of 1D NMR signals and 2D NMR correlations of isolated Cumyl-NBMEGACLONE acquired in acetone-d_6 at 500 MHz (^{1}H), 125 MHz (^{13}C).

Atom	δ (ppm)	Predicted Shift	COSY	HSQC	HMBC	H2BC	NOESY
1 C	109.23	109			7, 11		
2 C	125.84	126.21			8, 9		
3 C	139.36	140.43			7, 10, 25		
4 N	129.36						
5 C	145.29	127.2			12, 25		
7 C	122.09	122.07		7	10		
H	8.16	7.96	9	7	1, 3	9	
8 C	110.32	110		8	9	10	
H	7.54	7.37	10	8	2, 9		25
9 C	121.4	121.39		9	8	7, 10	
H	7.15	6.98	7, 10	9	2, 8		
10 C		124.17					
H	7.31	7.14	8, 9		3, 7	8, 9	
11 C	93	95.3		11	12	12	
H	6.72	6.73	12	11	1, 13		12, 25
12 C		132.84					
H	7.98	7.97	11		5, 11, 13, 14, 16	11	11, 17, 18
13 N	179.31				11, 12, 17, 18		
14 C	160.05	160.18			12		
15 O							
16 C	64.59	64.54			12, 17, 18, 20, 24		
17 C	30.05	30.03		17	18		
H3	2.02	1.98		17	13, 16, 18, 19		12, 24
18 C	30.07	30.03		18	17		
H3	2.02	2.03		18	13, 16, 17, 19		12, 20
19 C	149.26	149.05			17, 18, 21, 23		
20 C	125.06	124.9		20	22, 24		
H	7.22	7.22	21	20	16, 22, 24	21	18
21 C	128.87	128.82		21	23	20	
H	7.22	7.22	20, 22	21	19, 23		
22 C	126.5	126.62		22	20, 24		
H	7.15	7.35	21, 23	22	20, 24		
23 C	128.87	128.82		23	21	24	
H	7.22	7.22	22, 24	23	19, 21		
24 C	125.06	124.9		24	20, 22		
H	7.22	7.22	23	24	16, 20, 22	23	17
25 C	46.25	48.63		25	26, 27', 27"	26	
H2	4.38	4.20, 4.44	26	25	3, 5, 26, 27, 28	26	8, 11, 26
26 C	41.68	40.29		26	25, 27', 30	25, 27', 27", 28	
H	2.54	1.3	25, 27', 27", 28	26	25, 27, 28, 33	25, 27, 28	25
27 C	35.06	36.16		27', 27"	25, 26, 28, 30	26, 29	
H'	0.99	1.05, 1.30	26	27	25, 26, 28, 29, 31	26	
H"	1.66	1.05, 1.30	26, 29	27	25, 31	26, 29	
28 C	40	42.31		28	25, 26, 27', 29, 30, 33'	26, 30, 33'	
H	2.15	1.9	26, 30, 33'	28	27, 29, 31	26, 30, 33	
29 C	37.99	36.25		29	27', 28, 30, 31	27", 30	
H	2.21	2.14	27", 30, 31, 33'	29	28, 33	27, 30, 31	
30 C	40.47	38.09		30		28, 29	
H2	1.33	1.17, 1.42	28, 29	30	26, 27, 28, 29, 31, 33	28, 29	
31 C	31.01	28.27		31	27', 27", 28, 30, 33'	29, 33'	
H2	1.4	1.15, 1.40	29, 33'	31	29, 33	33	
33 C	23.42	28.18		33', 33"	26, 29, 30, 31	28, 31	
H'	1.48	1.24, 1.49	28, 29, 31	33	28, 31	28, 31	
H"	1.95	1.24, 1.49		33			

Figure S2: [1]H-NMR (500 MHz, 297 K, acetone-d_6) data of Cumyl-NBMINACA isolated from herbal blend material (purity >95%).

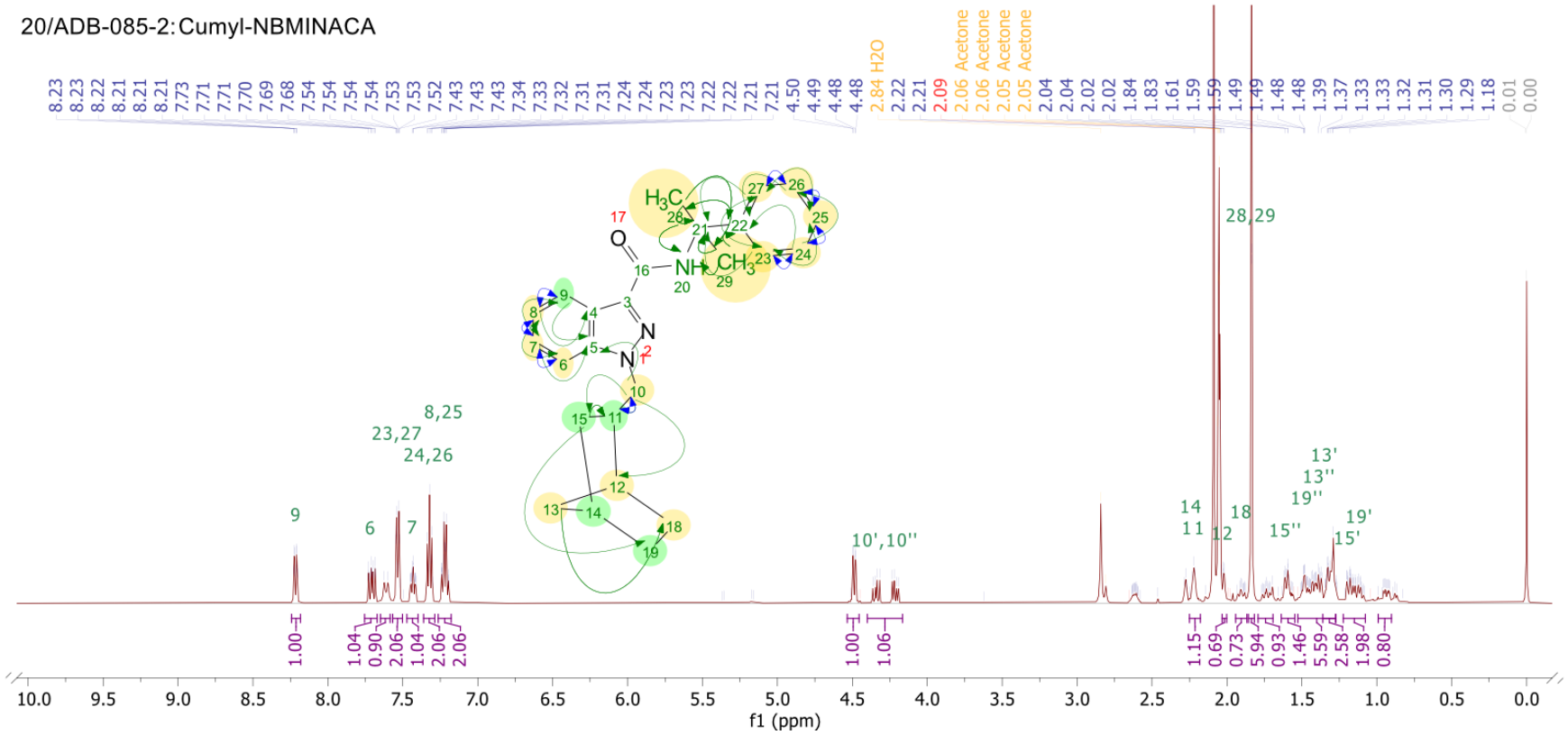

Table S2: Chemical shifts of 1D NMR signals and 2D NMR correlations of isolated Cumyl-NBMINACA acquired in acetone-d_6 at 500 MHz (^{1}H), 125 MHz (^{13}C).

Atom	δ (ppm)	Predicted Shift	COSY	HSQC	HMBC	H2BC	Atom	δ (ppm)	Predicted Shift	COSY	HSQC	HMBC	H2BC
3 C	139.46	135.65					16 C	162.22	161.78				
4 C	123.51	123.45			8		18 C	23.33	28.18		18	13', 13"	
5 C	142.07	141.02			7, 9, 10', 10"		H2	1.9	1.24, 1.49		18		
6 C	110.83	110.64		6	8	7	19 C	29.88	28.27		19', 19"	15"	
H	7.71	7,65	7	6	8	7	H'	1.12	1.15, 1.40		19		
7 C	127.35	127.08		7	9	6	H"	1.47	1.15, 1.40		19		
H	7.43	7.4	6.8	7	5, 9	6, 8	20 N	125.03					
8 C	122.99	123.07		8	6	7, 9	H						
H	7.22	7.22	7. 9	8	4, 6	9	21 C	56.4	56.05			23, 27, 28, 29	
9 C	123.31	122.97		9	7	8	22 C	149.06	148.54			24, 26, 28, 29	
H	8.21	8.23	8	9	5, 7	8	23 C	125.77	125.64		23	25, 27	24
10 C	54.26	56.1		10', 10"			H	7.54	7.52	24	23	21, 25, 27	24
H'	4.35	3.52, 3.77	10", 11	10	5, 11, 12, 15		24 C	128.93	128.72		24		23, 25
H"	4.22	3.52, 3.77	10', 11	10	5, 11, 12, 15		H	7.32	7.32	23, 25	24	22, 26	23
11 C	43.67	40.33			10', 10", 15', 15"		25 C	127.02	126.62		25	23, 27	
H	2.23	1.3	10', 10"				H	7.22	7.18	24, 26	25	23, 27	24
12 C	39.85	42.31		12	10', 10"		26 C	128.93	128.72		26	24	
H	2.03	2.31		12			H	7.32	7.32	25, 27	26	22	27
13 C	40.34	39.25		13', 13"			27 C	125.77	125.64		27	23, 25	26
H'	1.35	1.17, 1.42		13	18		H	7.54	7.52	26	27	21, 23, 25	
H"	1.39	1.17, 1.42		13	18		28 C	29.96	29.84		28	29	
14 C	37.82	36.25		14			H3	1.84	1.84		28	21, 22, 29	
H	2.24	2.14		14			29 C	29.96	29.84		29	28	
15 C	35.69	36.16		15', 15"	10', 10"		H3	1.84	1.84		29	21, 22, 28	
H'	1.19	0.95, 1.59		15	11								
H"	1.61	0.95, 1.59		15	11, 19								

Figure S3: Extracted-ion chromatogram (XIC) of one authentic urine sample containing Cumyl-CBMEGACLONE metabolites. Mass tolerance: 0.002 Da for all.

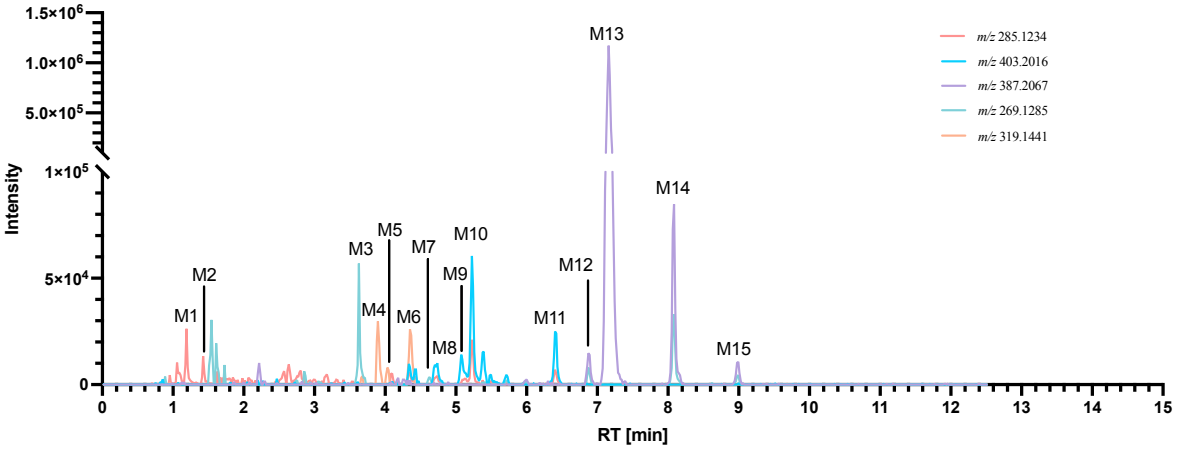

Figure S4: Extracted-ion chromatogram (XIC) of one pHLM assay containing in vitro generated Cumyl-CBMEGACLONE metabolites. Mass tolerance: 0.002 Da for all.

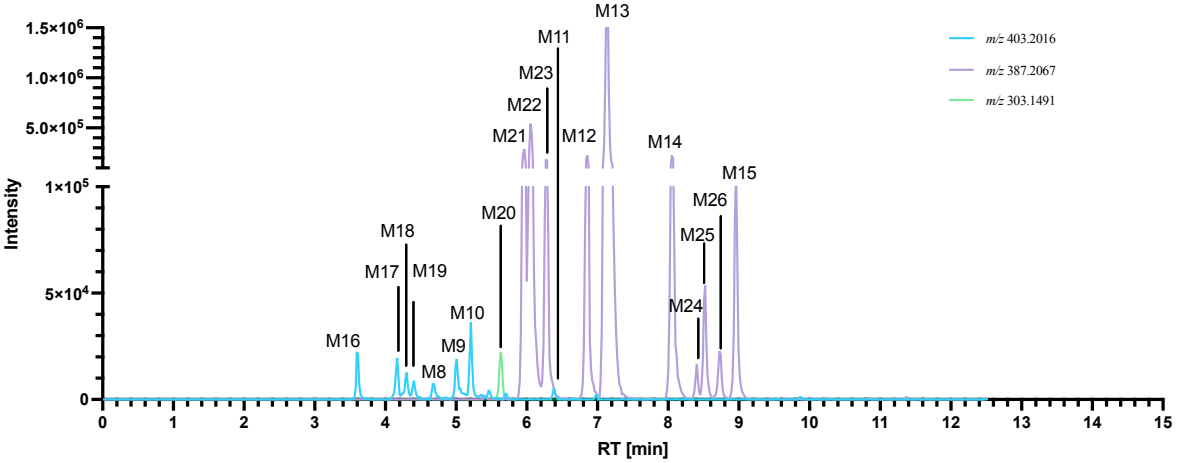

Figure S5: Spectra of metabolites of Cumyl-CBMEGACLONE, as obtained from the analysis of pHLM (by auto-MS/MS or bbCID). The metabolite the spectra of which is shown is underlined. Metabolites only generated in vitro are shown grouped together. m/z is shown as theoretical, colored and in italic, and experimental, bolded in black, just below.

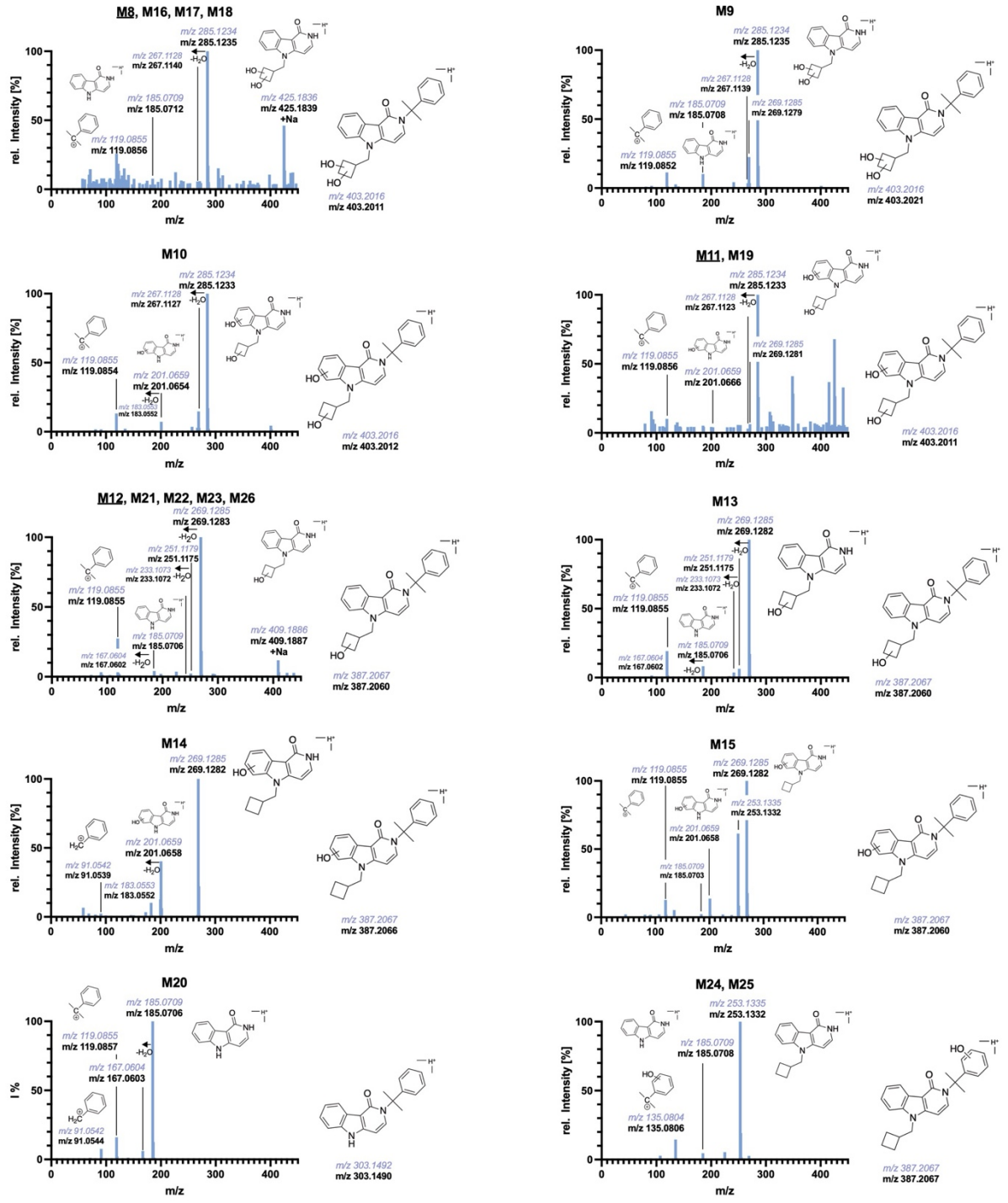

Figure S6: Extracted-ion chromatogram (XIC) of one authentic urine sample containing Cumyl-NBMEGACLONE metabolites. Mass tolerance: 0.002 Da for all.

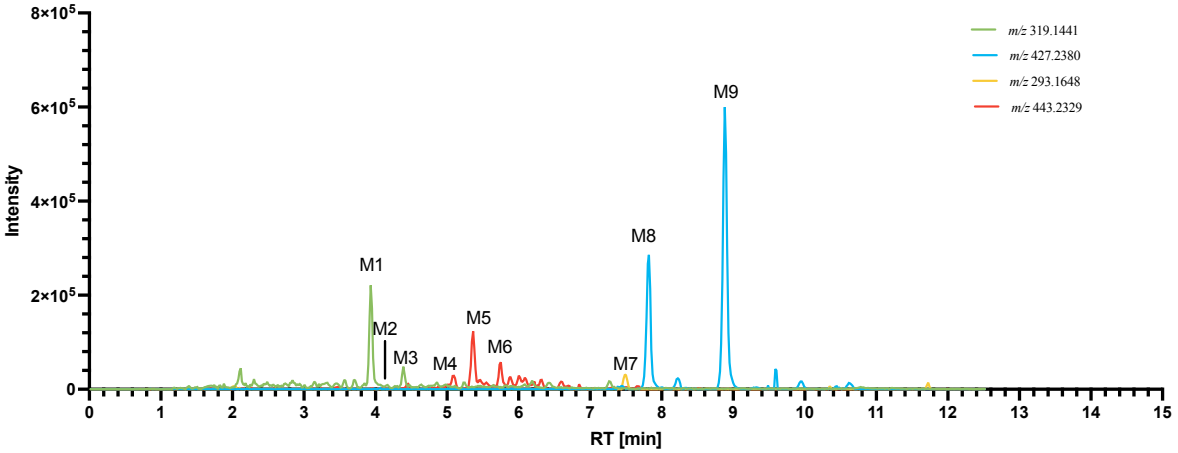

Figure S7: Extracted-ion chromatogram (XIC) of one pHLM assay containing in vitro generated Cumyl-NBMEGACLONE metabolites. Mass tolerance: 0.002 Da for all.

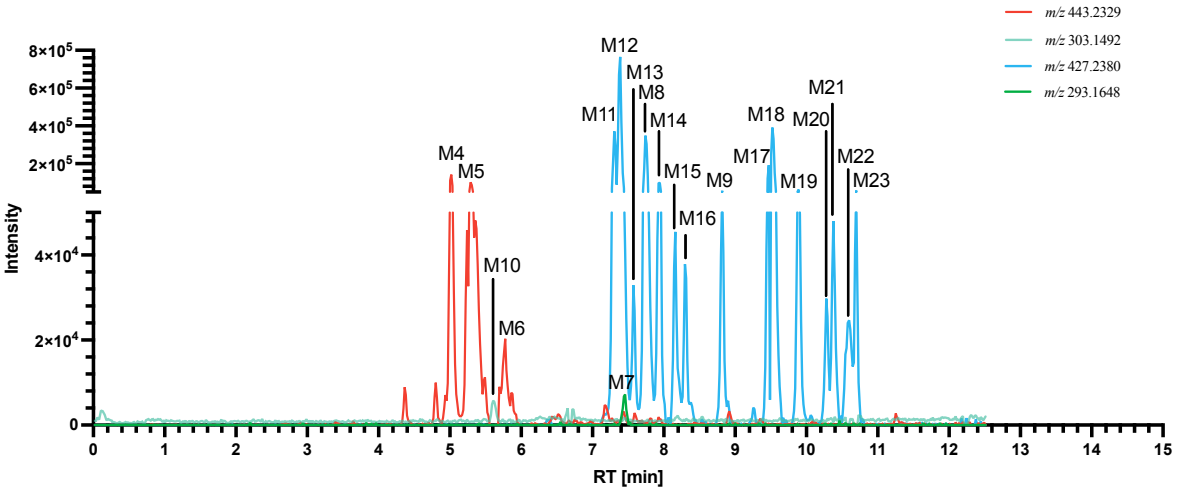

Figure S8: Spectra of metabolites of Cumyl-NBMEGACLONE, as obtained from the analysis of pHLM (by auto-MS/MS for M7, M11-23 or bbCID). Metabolites only generated in vitro are shown grouped together. m/z is shown as theoretical, colored and in italic, and experimental, bolded in black, just below.

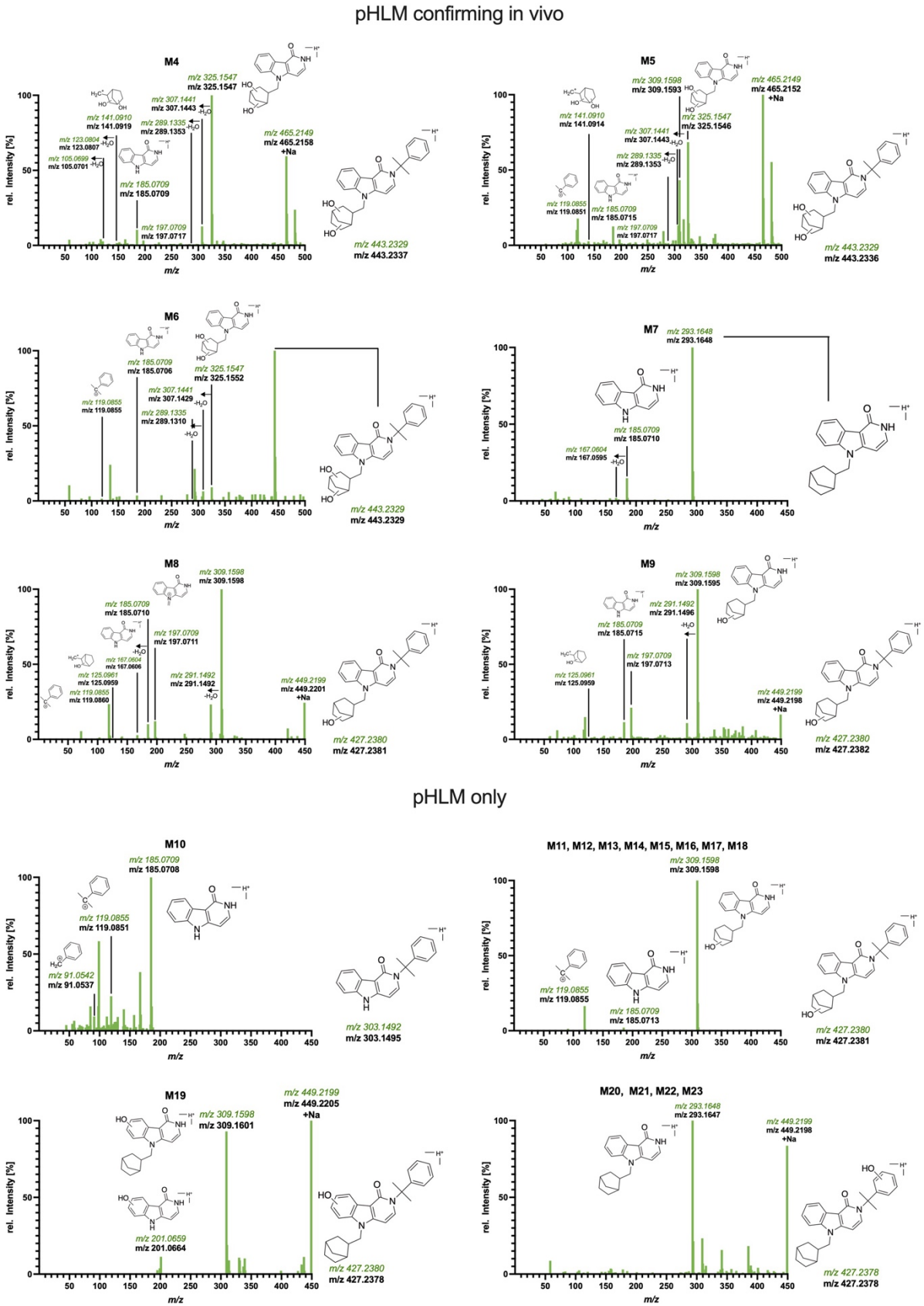

Figure S9: Extracted-ion chromatogram (XIC) of one authentic urine sample containing Cumyl-NBMINACA metabolites. Mass tolerance: 0.002 Da for all.

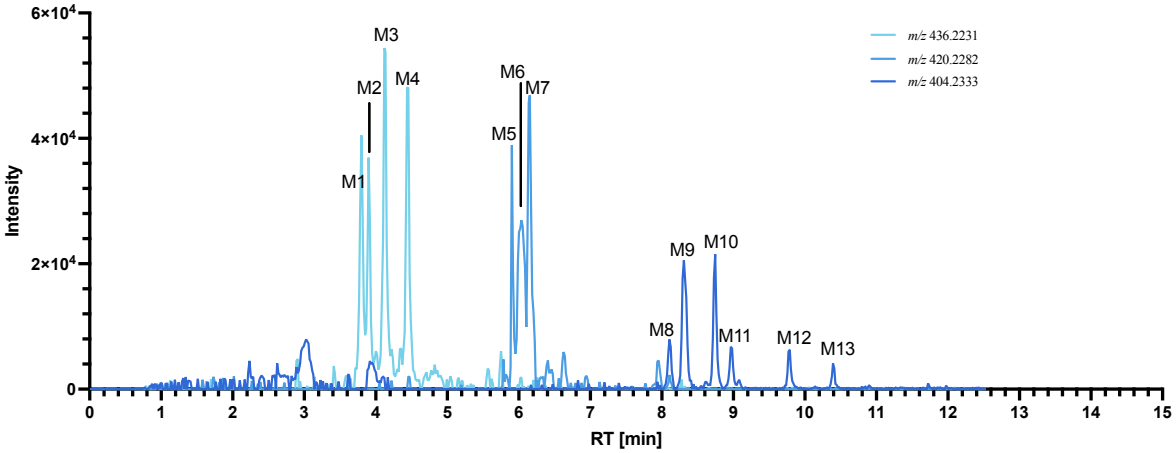

Figure S10: Extracted-ion chromatogram (XIC) of one pHLM assay containing in vitro generated Cumyl-NBMINACA metabolites. Mass tolerance: 0.002 Da for all.

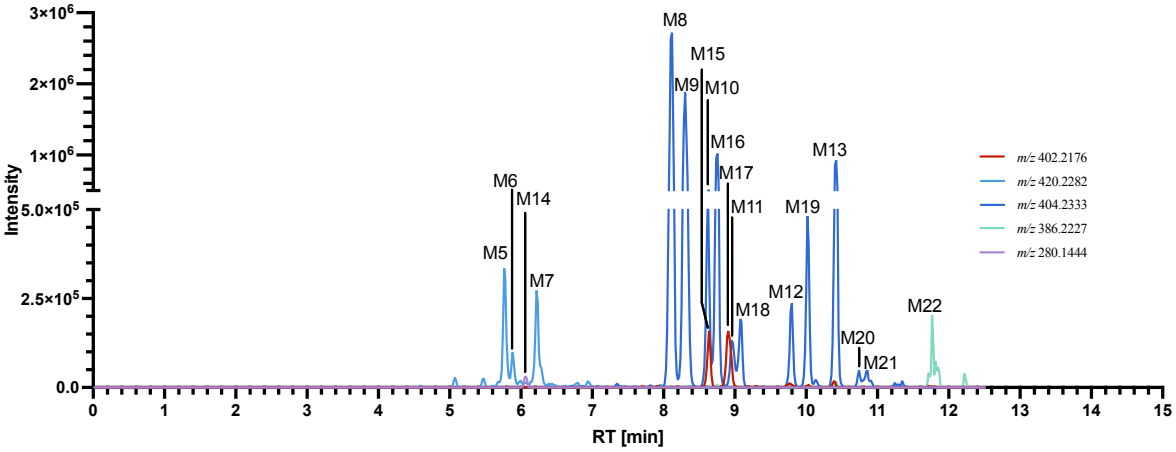

Figure S11: Spectra of metabolites of Cumyl-NBMINACA, as obtained from the analysis of pHLM (by bbCID). Metabolites only generated in vitro are shown grouped together. m/z is shown as theoretical, colored and in italic, and experimental, bolded in black, just below.