Supporting Information

Probing the Carboxyester Side Chain in Controlled Deactivation (-)-Δ^8-Tetrahydrocannabinols

Spyros P. Nikas,[†,§] Rishi Sharma,[†§] Carol A. Paronis,[†] Shashank Kulkarni,[†] Ganesh A. Thakur,[†] Dow Hurst,[£] JodiAnne T. Wood,[†] Roger S. Gifford,[†] Girija Rajarshi,[†], Yingpeng Liu,[†] Jimit Girish Raghav,[†] Jason Jianxin Guo,[†] Torbjörn U.C. Järbe,[†] Patricia H. Reggio,[£] Jack Bergman,[‡] and Alexandros Makriyannis.*[,†,#]

[†]Center for Drug Discovery and Departments of Chemistry and Chemical Biology and Pharmaceutical Sciences, Northeastern University, Boston, Massachusetts 02115, United States

[£]Center for Drug Discovery, University of North Carolina at Greensboro, Greensboro, North Carolina 27402, United States

[‡]McLean Hospital, Harvard Medical School, Belmont, Massachusetts 02478, United States

[#]King Abdulaziz University, Jeddah, 22254, Saudi Arabia

*To whom correspondence should be addressed.

[§]These two authors contributed equally to this work.

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Table S1: Elemental analyses

Compd.	Mol. Formula	Calcd.	Found
6b	$C_{24}H_{33}BrO_4$	C: 61.94; H: 7.15	C: 62.27; H: 7.53
7c	$C_{26}H_{33}NO_4$	C: 73.73; H: 7.85; N: 3.31	C: 73.47; H: 8.17; N: 3.66
9b	$C_{23}H_{31}BrO_4$	C: 61.20; H: 6.92	C: 60.95; H: 6.70
9d	$C_{27}H_{36}N_2O_4$	C: 71.65; H: 8.02; N: 6.19	C: 71.97; H: 8.31; N: 6.52
10a	$C_{24}H_{31}NO_4$	C: 72.52; H: 7.86; N: 3.52	C: 72.90; H: 8.08; N: 3.87
16	$C_{25}H_{36}O_4$	C: 74.96; H: 9.06	C: 75.28; H: 8.75

Molecular Modeling Supplemental Tables

Table S2. Top 20 Glide scores for 10a*

Conformer	Glide XP Score (kcal/mol)	Conform Cost (kcal/mol)	Total E (kcal/mol)
M0191	-5.0	4.0	-1.0
M0069	-5.0	2.0	-3.0
M0114	-4.9	4.0	-1.0
M0187	-4.8	2.0	-2.9
M0186	-4.7	4.0	-0.8
M0086	-4.7	0.7	-4.0
M0023	-4.6	1.1	-3.5
M0027	-4.6	1.1	-3.5
M0009	-4.5	0.7	-3.9
M0017	-4.5	1.0	-3.4
M0057	-4.5	1.7	-2.8
M0132	-4.5	1.8	-2.7
M0091	-4.4	2.8	-1.7
M0009	-4.4	0.7	-3.8
M0180	-4.4	2.8	-1.7
M0086	-4.4	0.7	-3.8
M0001	**-4.4**	**0.1**	**-4.3**
M0051	-4.4	1.8	-2.6
M0070	-4.4	2.0	-2.4
M0191	-4.3	4.0	-0.4
M0016	-4.3	1.0	-3.3

* Conformer from the bolded row was taken forward with a post Glide minimization and ligand/receptor interaction energies.

Table S3. Top 20 Glide scores for (-)-Δ^8-THC-DMH*

Conformer	Glide XP Score (kcal/mol)	Conform Cost (kcal/mol)	Total E (kcal/mol)
M0044	-5.6	1.2	-4.4
M0007	**-5.5**	**0.2**	**-5.4**
M0456	-5.5	1.2	-4.3
M0007	-5.4	0.2	-5.2
M0435	-5.2	1.2	-4.1
M0047	-5.2	1.2	-4.1
M0355	-5.1	1.2	-3.9
M0055	-5.1	1.2	-3.9
M0150	-5.1	2.3	-2.7
M0196	-5.0	2.1	-2.9
M0696	-5.0	5.1	0.2
M0035	-4.9	1.0	-3.9
M0395	-4.9	4.0	-0.9
M0328	-4.9	3.9	-1.0
M0003	-4.8	0.0	-4.8
M0338	-4.8	4.1	-0.8
M0436	-4.8	4.1	-0.7
M0003	-4.8	0.0	-4.8
M0269	-4.8	3.1	-1.7
M0521	-4.7	4.8	0.1
M0177	-4.7	2.0	-2.8

*Conformer from the bolded row was taken forward with a post Glide minimization and ligand/receptor interaction energies.

Table S4. Top 20 Glide scores for (-)-Δ^8-THC*

Conformer	Glide XP Score (kcal/mol)	Conform Cost (kcal/mol)	Total E (kcal/mol)
M0243	-5.9	1.6	-4.4
M0122	-5.9	1.7	-4.2
M0023	-5.8	1.5	-4.2
M0080	**-5.7**	**0.0**	**-5.7**
M0203	-5.6	1.5	-4.1
M0901	-5.6	1.3	-4.3
M0934	-5.5	1.0	-4.5
M0391	-5.5	0.2	-5.3
M0107	-5.4	2.1	-3.3
M0134	-5.3	0.5	-4.7
M0040	-5.3	1.9	-3.4
M0198	-5.2	1.2	-4.0
M0102	-5.2	0.6	-4.6
M0268	-5.0	1.3	-3.7
M1000	-4.9	1.6	-3.3
M0351	-4.9	2.2	-2.7
M0938	-4.8	1.9	-2.9
M0127	-4.8	0.6	-4.2
M0040	-4.8	1.9	-2.9
M0060	-4.7	2.1	-2.7
M1000	-4.7	1.6	-3.1

* Conformer from the bolded row was taken forward with a post Glide minimization and ligand/receptor interaction energies.

Table S5. Ligand/Receptor Interaction Energies for 10a**

Residues	Electrostatic (kcal/mol)	Van der Waals (kcal/mol)	Total Energy (kcal/mol)
S1.39(123)	0.0	-0.1	-0.1
S2.60(173)	0.0	-0.1	-0.1
F2.64(177)	0.0	-0.6	-0.6
F2.67(180)	0.0	-0.1	-0.1
F3.25(189)	-0.1	**-2.8**	**-2.9**
K3.28(192)	**-4.5**	-1.0	**-5.5**
L3.29(193)	0.4	**-3.5**	**-3.2**
V3.32(196)	-0.1	**-2.0**	**-2.0**
T3.33(197)	**-6.5**	1.8	**-4.7**
F3.36(200)	-0.2	-1.6	-1.8
N(256)	-0.1	-0.5	-0.5
F(268)	-0.3	**-3.1**	**-3.4**
P(269)	-0.3	-0.7	-0.9
Y5.39(275)	-0.1	-0.2	-0.3
L5.40(276)	-0.1	-0.7	-0.8
W5.43(279)	-0.1	-0.9	-0.9
W6.48(356)	0.0	-0.1	-0.1
L6.51(359)	0.0	-1.1	-1.0
M6.55(363)	-0.2	**-2.2**	**-2.3**
D6.58(366)	1.4	-0.5	1.0
M(371)	-0.1	**-2.4**	**-2.5**
N(372)	-0.1	-0.8	-0.8
K(373)	0.0	-0.5	-0.5
I(375)	0.1	-0.8	-0.7
F7.35(379)	-0.1	-1.7	-1.9
A7.36(380)	0.0	-0.6	-0.6
C7.38(382)	0.0	-0.6	-0.6
S7.39(383)	0.2	**-3.2**	**-3.0**
C7.42(386)	-0.1	**-2.2**	**-2.4**
	-10.6	**-32.5**	**-43.1**

**Interaction energies equal to -2.0 kcal/mol or better are shown in bold

Table S6. Ligand/Receptor Interaction Energies for (-)-Δ^8-THC-DMH**

Residues	Electrostatic (kcal/mol)	Van der Waals (kcal/mol)	Total Energy (kcal/mol)
F2.64(177)	0.0	-0.5	-0.5
F2.67(180)	0.0	-0.1	-0.1
F3.25(189)	0.0	**-2.9**	**-2.9**
K3.28(192)	**-5.6**	-0.3	**-5.8**
L3.29(193)	-0.1	**-4.7**	**-4.7**
V3.32(196)	0.1	-1.8	-1.7
T3.33(197)	-0.1	**-2.8**	**-2.8**
F3.36(200)	0.0	-1.6	-1.6
P4.60(251)	0.0	-0.3	-0.3
N(256)	-0.1	-1.0	-1.2
F(268)	0.0	**-2.7**	**-2.7**
P(269)	0.0	-0.3	-0.3
Y5.39(275)	0.0	-1.2	-1.1
L5.40(276)	0.0	-1.1	-1.1
W5.43(279)	0.0	-1.2	-1.2
L6.51(359)	0.0	-0.9	-0.9
I6.54(362)	0.0	-0.1	-0.1
M6.55(363)	0.0	**-3.1**	**-3.2**
M(371)	-0.1	**-2.1**	**-2.2**
N(372)	-0.1	-0.6	-0.7
K(373)	0.0	-0.4	-0.5
I(375)	0.0	-0.5	-0.5
F7.35(379)	-0.1	**-2.0**	**-2.1**
A7.36(380)	0.0	-0.6	-0.6
C7.38(382)	0.0	-0.7	-0.6
S7.39(383)	0.2	**-3.3**	**-3.1**
C7.42(386)	-0.1	**-2.1**	**-2.2**
	-5.8	**-38.8**	**-44.6**

**Interaction energies equal to -2.0 kcal/mol or better are shown in bold

Table S7. Ligand/Receptor Interaction Energies for (-)-Δ^8-THC**

Residues	Electrostatic (kcal/mol)	Van der Waals (kcal/mol)	Total Energy (kcal/mol)
I1.35(119)	0.0	-0.1	-0.1
F2.64(177)	0.0	-0.7	-0.6
F2.67(180)	0.0	-0.4	-0.3
F3.25(189)	0.0	**-2.6**	**-2.7**
K3.28(192)	**-5.9**	1.2	**-4.7**
L3.29(193)	-0.1	**-2.0**	**-2.1**
V3.32(196)	0.1	-1.7	-1.5
T3.33(197)	0.0	-1.9	-1.9
F3.36(200)	0.1	-1.5	-1.4
T3.37(201)	0.0	-0.2	-0.1
F(268)	0.0	**-2.1**	**-2.1**
W5.43(279)	0.0	-1.1	-1.1
W6.48(356)	0.0	-0.1	-0.1
L6.51(359)	0.0	-0.5	-0.5
M6.55(363)	0.1	-1.6	-1.5
M(371)	0.0	**-2.6**	**-2.6**
N(372)	-0.2	-1.8	-1.9
K(373)	-0.1	-1.4	-1.5
I(375)	0.1	-1.2	-1.1
F7.35(379)	-0.1	-1.6	-1.7
A7.36(380)	0.0	-0.8	-0.8
C7.38(382)	-0.1	-0.5	-0.5
S7.39(383)	0.0	**-3.0**	**-2.9**
C7.42(386)	-0.1	-1.6	-1.7
	-6.2	**-29.5**	**-35.7**

**Interaction energies equal to -2.0 kcal/mol or better are shown in bold

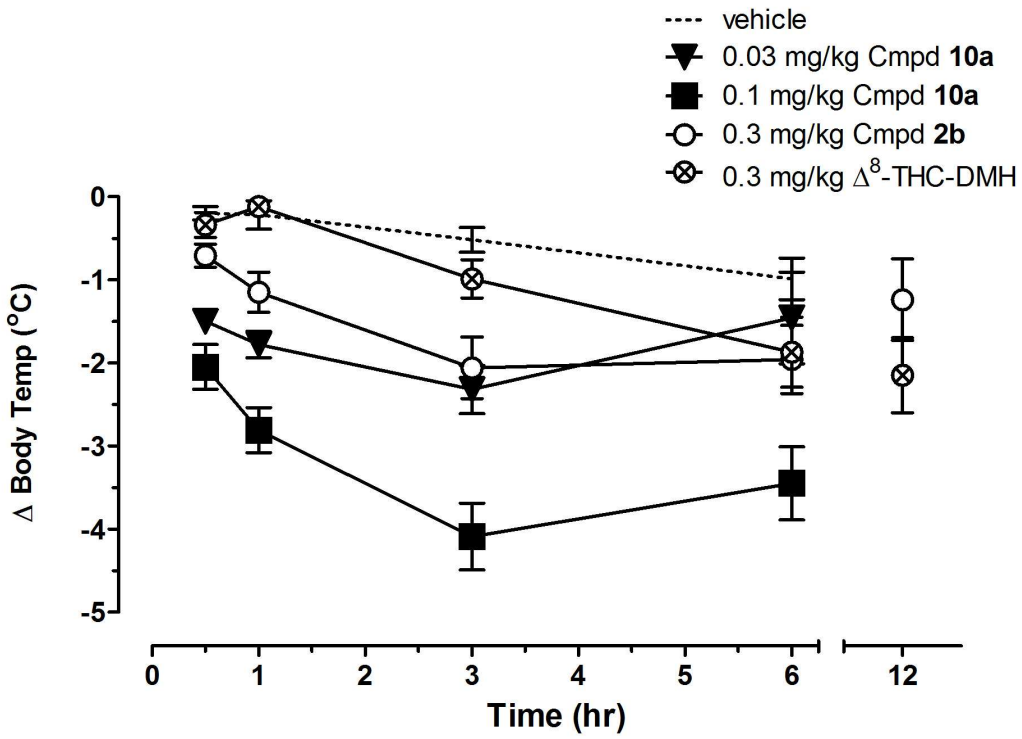

Figure S1: Hypothermic effects of approximately equivalent doses of **10a**, **2b**, and Δ^8-THC-DMH at different times after injection; the dotted line represents average temperature changes after vehicle injection. Abscissa: time (in minutes) after injection; ordinate; change in body temperature.

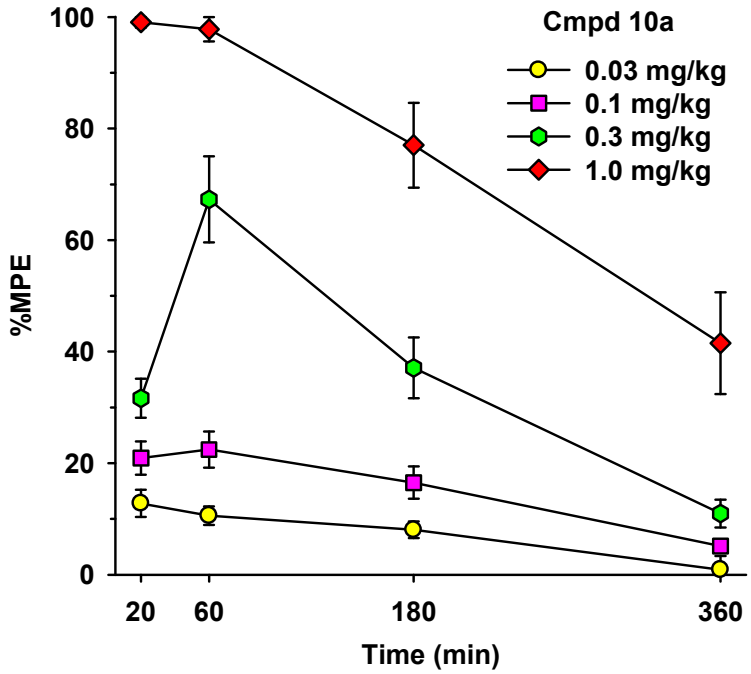

Figure S2: Tail-flick latencies in a hot water-bath (52^{o}C) after administration of four doses of compound **10a** examined at four time-points (20, 60, 180, and 360 min post-administration) using male CD-1 mice. Abscissa: time (min) after injection; ordinate; tail-flick withdrawal latencies expressed as a percentage of maximum possible effect (% MPE; group mean ± sem). A two-way repeated measures ANOVA indicated significance for Dose (D) [$F_{3, 20} = 125.1$], Time (T) [$F_{3, 60} = 61.4$] and the interaction D x T [$F_{9, 60} = 10.8$].