SUPPLEMENTAL MATERIAL

Xiong et al., http://www.jem.org/cgi/content/full/jem.20120242/DC1

Chemical synthesis. DH-CBD, DD-CBD, 1-desoxy-THC, and K071 were synthesized after the procedure as described previously (Xiong et al., 2011).

Synthesis of CBD analogues. Proton nuclear magnetic resonance (^{1}H NMR, 500 MHz) and carbon nuclear magnetic resonance (^{13}C NMR, 500 MHz) spectra were recorded on a Bruker-500 instrument in $CDCl_3$ (unless otherwise noted) with the values given in ppm (TMS as internal standard) and *J* (Hz) assignments of ^{1}H resonance coupling. The high resolution electrospray ionization (ESI) mass spectra were obtained on a Waters LCT Premier time-of-flight (TOF) mass spectrometer. Thin-layer chromatography (TLC) was performed on 0.25 mm Analtech GHLF silica gel. Flash column chromatography was performed with Bodman silica gel LC 60 A. Elemental analyses were performed by Atlantic Microlabs, Inc.

***p*-Mentha-1,8-dien-3-yl 3-*n*-pentylphenyl ether (K065, 3)[2].** A solution of (+)-trans-*p*-Menthadien-(2,8)-ol (945 mg, 6.21 mmol), *m*-pentyl phenol [1](926 mg, 5.64 mmol), and *N*,*N*-Dimethylformamid-dinopentylacetal (1.69 g, 7.34 mmol) in 33 ml anhydrous methylene chloride was stirred for 3 d at room temperature (20°C). The mixture was condensed and the crude product was purified by column chromatography on silica using Hexanes/Benzene (10:1) as a mobile phase to give the less polar product 2 as a colorless oil (710 mg, 43% based on *m*-pentyl phenol): $[a]_D^{20} = -114.9°$ (c, 0.736, CHCl3); ^{1}H NMR (CDCl3): 7.17 (t, 1H, *J* = 7.5 Hz), 6.70–6.77 (m, 3H), 5.57 (s, 1H), 4.83 (t, 1H, *J* = 1.5 Hz), 4.80 (s, 1H), 4.77 (br, 1H), 2.57 (t, 2H, *J* = 7.5 Hz), 2.44–2.48 (m, 1H), 2.08–2.15 (m, 1H), 1.95–2.04 (m, 1H), 1.82–1.88 (m, 1H), 1.77 (s, 3H), 1.72 (s, 3H), 1.58–1.66 (m, 3H), 1.30–1.38 (m, 4H), 0.90 (t, 3H, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$): δ 158.05, 146.41, 144.60, 138.99, 129.08, 120.73, 120.64, 116.04, 112.47, 111.00, 75.15, 46.04, 35.96, 31.52, 30.8, 29.62, 26.01, 23.26, 22.52, 21.35, 14.01 ppm; m/z: HRMS (ESI) calculated for C21H31O (M+H)+: 299.2375; found, 299.2371.

2-((1*R*,6*R*)-3-Methyl-6-(prop-1-en-2-yl)cyclohex-2-enyl)-5-(2-hydroxyl)ethylphenol (K266, 5)[2]. A solution of (+)-trans-*p*-Menthadien-(2,8)-ol (2, 550 mg, 3.61 mmol), *m*-(2-hydroxyl)ethyl phenol (452 mg, 3.27 mmol), and *N*,*N*-Dimethylformamid-dinopentylacetal (972 mg, 4.20 mmol) in 20 ml anhydrous methylene chloride was stirred for 3 d at room temperature (20°C). The mixture was condensed and the crude product was purified by column chromatography on silica using hexanes/ethyl acetate (6:4) as a mobile phase to give product as a colorless oil (98 mg, 11% based on *m*-(2-hydroxy)ethyl phenol); $[a]_D^{20} = -99.4°$ (c, 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$): 6.93 (d, 1H, *J* = 7.5 Hz), 6.64–6.70 (m, 2H), 5.75 (s, 1H), 5.47 (s, 1H), 4.65 (s, 1H), 4.56 (s, 1H), 3.80–3.84 (m, 2H), 3.42–3.46 (m, 1H), 2.78 (t, 2H, *J* = 7.0 Hz), 2.29–2.38 (m, 1H), 2.13–2.26 (m, 1H), 2.03–2.10 (m, 1H), 1.78 (s, 3H), 1.70–1.85 (m, 2H), 1.65 (br-s, 1H), 1.60 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 154.41, 148.49, 137.92, 137.80, 130.45, 128.42, 124.26, 121.00, 116.96, 111.09, 63.64, 47.35, 43.06, 38.82, 30.44, 28.48, 23.73, 20.73 ppm; m/z: HRMS (ESI) calculated for $C_{18}H_{25}O_2$ $(M+H)^+$: 273.1855; found, 273.1862.

2-((1*R*,6*R*)-3-Methyl-6-(prop-1-en-2-yl)cyclohex-2-enyl)-5-chlorophenol (K271, 7)[2]. A solution of (+)-trans-*p*-Menthadien-(2,8)-ol (550 mg, 3.61 mmol), *m*-(2-hydroxyl)ethyl phenol (420 mg, 3.27 mmol), and *N*,*N*-Dimethylformamid-dinopentylacetal (972 mg, 4.20 mmol) in anhydrous methylene chloride (15 ml) was stirred for 3 d at room temperature (20°C). The mixture was condensed and the crude product was purified by column chromatography on silica using hexanes: ethyl acetate (10:1) as a mobile phase to give product as a colorless oil (130 mg, 15% based on *m*-chlorophenol); $[a]_D^{20} = -108.2°$ (c, 2.20, $CHCl_3$); ^{1}H NMR ($CDCl_3$): 6.83–6.94 (m, 1H), 6.76–6.84 (m, 2H), 5.68 (s, 1H), 5.48 (s, 1H), 4.68 (s, 1H), 4.54 (s, 1H), 3.38–3.46 (m, 1H), 2.25–2.33 (m, 1H), 2.18–2.26 (m, 1H), 2.03–2.13 (m, 1H), 1.79 (s, 3H), 1.70–1.85 (m, 2H), 1.60 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 152.69, 152.43, 148.54, 128.76, 127.67, 126.80, 118.76, 118.65, 113.27, 113.12, 44.76, 37.35, 30.09, 28.86, 24.72, 22.74 ppm; m/z: HRMS (ESI) calculated for $C_{16}H_{20}ClO$ $(M+H)^+$: 263.1203; found, 263.1196.

2-((1*R*,6*R*)-3-Methyl-6-(prop-1-en-2-yl)cyclohex-2-enyl)-4-(2-hydroxyl)ethylphenol (K272, 9)[2]. A solution of (+)-trans-*p*-Menthadien-(2,8)-ol (550 mg, 3.61 mmol), *p*-(2-hydroxyl)ethyl phenol (452 mg, 3.27 mmol), and *N*,*N*-Dimethylformamid-dinopentylacetal (972 mg, 4.20 mmol) in 20 ml anhydrous methylene chloride was stirred for 3 d at room temperature (20°C). The mixture was condensed and the crude product was purified by column chromatography on silica using hexanes/ethyl acetate (6:4) as a mobile phase to give product as a colorless oil (98 mg, 11% based on *p*-(2-hydroxy)ethyl phenol); $[a]_D^{20} = -79.9°$ (c, 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$): 6.93 (d, 1H, *J* = 8.0, 2.0 Hz), 6.82 (d, 1H, *J* = 2.0 Hz), 6.74 (d, 1H, *J* = 8.0 Hz), 5.68 (s, 1H), 5.47 (s, 1H), 5.51 (s, 1H), 4.64 (s, 1H), 4.51 (s, 1H), 3.73–3.82 (m, 2H), 3.42–3.48 (m, 1H), 2.75 (t, 2H, *J* = 6.5 Hz), 2.30–2.37 (m, 1H), 2.16–2.28 (m, 1H), 2.03–2.10 (m, 1H), 1.78 (s, 3H), 1.70–1.85 (m, 2H), 1.60 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 153.08, 148.46, 131.05, 130.10, 128.07, 123.99, 116.74, 115.57, 111.18, 64.05, 47.38, 43.72, 38.43, 30.48, 28.41, 23.76, 20.50 ppm; m/z: HRMS (ESI) calculated for $C_{18}H_{25}O_2$ $(M+H)^+$: 273.1855; found, 273.1860.

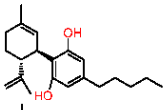
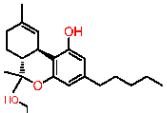
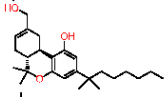
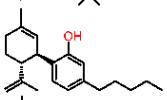
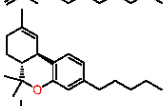
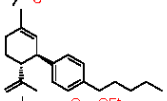
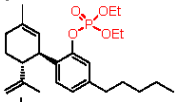
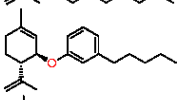
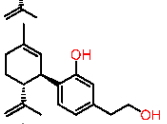
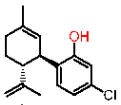
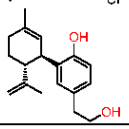
Chemical name	Chemical structure	CB_1 K_i values	CB_2 K_i values	Potentiation (1 μM)	EC_{50} of potentiation	Changes of PWL
		μM	*μM*	*%*	*μM*	*%*
CBD		4.77 ± 1.06	2.86 ± 0.81	501 ± 113	2.65 ± 0.79	101 ± 15
THC		0.031 ± 0.008	0.064 ± 0.017	965 ± 128	2.40 ± 0.14	186 ± 31
HU210		0.028 ± 0.005	0.61 ± 0.22	1095 ± 244	1.85 ± 0.26	156 ± 38
DH-CBD		8.36 ± 2.27	0.15 ± 0.21	980 ± 131	2.30 ± 0.16	190 ± 42
1-desoxy-THC		4.33 ± 1.20	0.050 ± 0.039	850 ± 200	3.62 ± 0.71	161 ± 27
DD-CBD		511 ± 168	16.57 ± 5.17	42 ± 24	>200	10 ± 16
K071		4.6 ± 1.9	2.17 ± 0.85	782 ± 103	2.98 ± 0.51	84 ± 25
K065		1.1 ± 0.23	>30	270 ± 112	5.62 ± 0.56	30 ± 22
K266		10.6 ± 3.6	0.58 ± 0.44	18 ± 18	>200	17 ± 20
K271		23.8 ± 8.7	39.17 ± 12.8	355 ± 45	4.39 ± 1.22	56 ± 30
K272		10.0 ± 6.2	1.65 ± 0.98	247 ± 74	8.79 ± 2.26	37 ± 29

Figure S1. Structural and functional relationships of 11 cannabinoids.

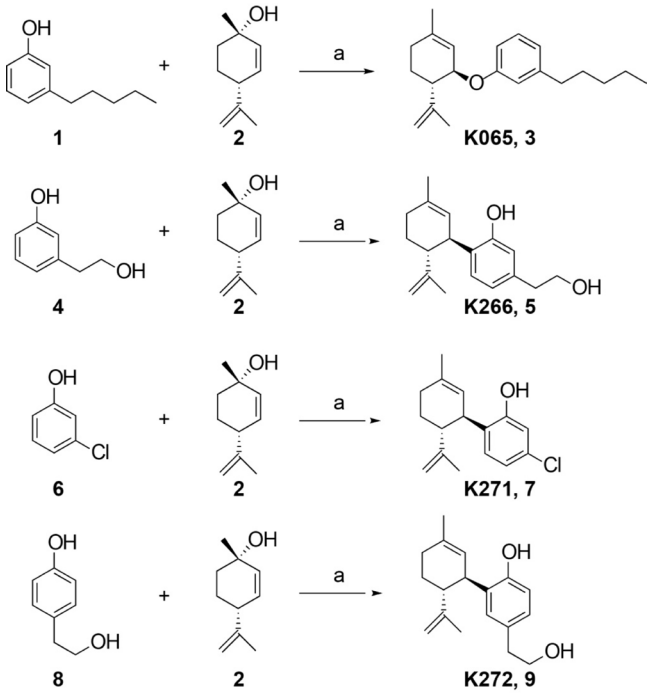


Figure S2. Schematic illustration of synthesis of CBD analogies. Reagents and conditions: (a) DMF-dineopentyl acetal, DCM, at room temperature for 3 d.