

Supplementary Materials

Theoretical study of the structural stability, chemical reactivity, and protein interaction for NMP compounds as modulators of the endocannabinoid system.

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Table S1. Experimental and calculated ^1H NMR δ (ppm) at BP86/cc-pVTZ level of theory in chloroform for NMP compounds.

	Groups	Exp. [9, 10]	CHCl_3
NMP-4	H_{ring}	6.86-8.07	6.98-8.18
	$\text{H}_{\text{CH}_3\text{-O}}$	3.93	3.89-4.11
	$\text{H}_{\text{R-CH}_2\text{-N}}$	4.22	4.24-4.37
	$\text{H}_{\text{R-CH}_2\text{-N}^*}$	3.71	2.55-4.97
	$\text{H}_{\text{R-CH}_2\text{-R}^{**}}$	1.62-1.69	1.50-1.99
	H_{CH_2}	1.35-1.85	1.40-1.76
	H_{CH_3}	0.88	0.94-1.21
	R²		0.9740
NMP-7	H_{ring}	7.23-8.19	7.51-8.33
	$\text{H}_{\text{R-CH}_2\text{-N}}$	4.25	4.42-4.43
	$\text{H}_{\text{R-CH}_2\text{-N}^*}$	3.73	2.60-5.05
	$\text{H}_{\text{R-CH}_2\text{-R}^{**}}$	1.61-1.67	1.60-2.07
	H_{CH_2}	1.32-1.83	1.40-1.83
	H_{CH_3}	0.85	0.94-1.22
	R²		0.9769
NMP-181	H_{ring}	7.23-8.81	7.56-9.00
	$\text{H}_{\text{CH}_2\text{-O}}$	4.48	4.15-4.71
	$\text{H}_{\text{R-CH}_2\text{-N}}$	4.21	4.42-4.43
	$\text{H}_{\text{CH}_2\text{-N}}$	2.76	2.52-3.17
	$\text{H}_{\text{CH}_3\text{-N}}$	2.36	1.73-2.83
	H_{CH_2}	1.26-1.81	1.44-1.87
	H_{CH_3}	0.84	0.93-1.21
	R²		0.9928

*cicloalkane; **cyclic

Table S2. Experimental and calculated ^{13}C NMR δ (ppm) at BP86/cc-pVTZ level of theory in chloroform for NMP compounds.

	Groups	Exp. [10,11]	CHCl_3
NMP-4	$\text{C}=\text{O}$	171.7	174.2
	$\text{C}-\text{OCH}_3$	159.5	164.4
	$\text{C}=\text{N}-\text{R}$	141.3-142.4	143.8-144.8
	C_{ring}	119-127	121.0-131.0
	CCH_2ring	93.6 -121.4	96.9-128.3
	CCH_3-O		58.5
	CCH_2-C^*	24.9-28.6	29.4-31.1
	CCH_2-N^*	43.3-55.8	47.3-54.7
	CCH_2-N		47.4
	CCH_2-C	22.6 - 29.5	29.4-34.9
	CCH_3-C	14.11	16.5
	R^2		0.9977
NMP-7	$\text{C}=\text{O}$	171.5	173.2
	$\text{C}=\text{N}-\text{R}$	140.9-141.0	143.0-143.5
	C_{ring}	125.1-126.7	124.1-131.1
	CH_2ring	108.4-122.4	110.0-130.4
	CCH_2-C^*	29.4	30.0-31.0
	CCH_2-N^*		47.4-54.0
	CCH_2-N	43.2	48.1
	CCH_2-C	22.5-28.7	29.5-35.1
	CCH_3-C	14.0	16.6
	R^2		0.9799
NMP-181	$\text{C}=\text{O}$	167.5	171.3
	$\text{C}=\text{N}-\text{R}$	141.0-143.1	143.8-145.0
	C_{ring}	120.7-122.6	123.6-126.5
	CH_2ring	108.2-127.4	109.7-130.2
	CCH_2-O	58.1	69.0
	CCH_3-N	46.04	47.0-51.7
	CCH_2-N	43.3-62.9	48.5-62.8
	CCH_2-C	22.5-29.4	29.5-35.3
	CCH_3-C	14.0	16.6
	R^2		0.9732

Table S3. Theoretical IR frequencies (in cm⁻¹) and PED (≥10%) at BP86/cc-pVTZ level of theory in chloroform for NMP compounds using the scale factor of 1.014. ν refers to stretching vibrational mode, β refers to in plane bending vibrational mode, and τ refers to torsional vibrational mode.

	Freq	Int	Freq esc	PED (≥ 10%)
NMP-4	3063.1	6.07	3106.0	ν CH(91)
	3012.2	22.23	3054.3	ν CH(86)
	2997.4	22.19	3039.3	ν CH(91)
	2949.7	9.33	2991.0	ν CH(90)
	2939.3	9.79	2980.5	ν CH(86)
	2935.4	24.78	2976.5	ν CH(91)
	1612.4	55.73	1635.0	ν CC(50)
	1600.8	88.20	1623.2	ν OC(77)
	1221.9	29.54	1239.0	ν OC(13)
	577.0	12.69	585.0	β OCC(13)
NMP-7	3118.7	7.41	3162.3	ν CH(93)
	3013.5	25.38	3055.7	ν CH(93)
	2997.3	23.28	3039.3	ν CH(83)
	2951.5	10.61	2992.8	ν CH(90)
	2947.7	10.72	2989.0	ν CH(88)
	2939.8	10.99	2980.9	ν CH(86)
	1607.0	17.17	1629.5	ν CC(33)
	1597.2	100.00	1619.5	ν OC(75)
	1396.9	98.81	1416.5	ν NC(29)+ β HNC(32)
	1331.3	37.90	1349.9	ν NC(26)
NMP-181	3119.9	4.91	3163.6	ν CH(93)
	3036.8	6.81	3079.3	ν CH(94)
	3013.4	12.14	3055.6	ν CH(75)
	2939.9	7.52	2981.0	ν CH(87)
	2836.9	49.51	2876.6	ν CH(98)
	1668.8	100.00	1692.1	ν OC(85)
	1606.9	14.75	1629.4	ν CC(39)
	1246.3	4.43	1263.7	ν NC(15) + τ HCNC(31)
	1190.5	80.04	1207.1	ν OC(11)+ ν CC(12)+ β CC C(12)
	1073.5	47.18	1088.5	ν OC(24)

Table S4. Selected bond lengths (Å), valence angles and dihedral angles (degrees) for the NMP compounds at BP86/cc-pVTZ level of theory in chloroform solvent.

Compound	E _{HOMO}	E _{LUMO}	ΔE_{gap}
NMP-4	-5.024	-1.855	3.169
NMP-7	-5.137	-1.996	3.142
NMP-181	-5.125	-2.122	3.002

Table S5. Molecular orbital contribution percentages of the NMP compounds at BP86/cc-pVTZ level of theory in chloroform.

	MO	eV	Carbazole	Pentyl	Carbonyl	Piperidine	Methoxy	
NMP-4	106	L+3	-0.16	82	4	7	4	3
	105	L+2	-0.79	85	2	9	3	1
	104	L+1	-1.49	70	0	22	8	0
	103	LUMO	-1.85	95	1	1	1	3
	102	HOMO	-5.02	80	3	8	1	9
	101	H-1	-5.19	89	3	0	0	8
	100	H-2	-5.57	6	0	46	47	1
	99	H-3	-5.86	18	0	50	30	2
	MO	eV	Carbazole	Pentyl	Carbonyl	Piperidine		
NMP-7	98	L+3	-0.37	92	2	3	2	
	97	L+2	-0.82	88	2	7	3	
	96	L+1	-1.55	70	1	22	8	
	95	LUMO	-2.00	97	1	1	1	
	94	HOMO	-5.14	86	5	7	2	
	93	H-1	-5.5	65	0	27	8	
	92	H-2	-5.64	26	0	23	51	
	91	H-3	-5.94	30	0	50	19	
	MO	eV	Carbazole	Pentyl	Ester	Amine		
NMP-181	99	L+3	-0.43	95	3	2	0	
	98	L+2	-0.92	94	2	4	0	
	97	L+1	-1.99	83	1	16	0	
	96	LUMO	-2.12	76	0	23	0	
	95	HOMO	-5.12	0	0	2	97	
	94	H-1	-5.29	90	6	4	0	
	93	H-2	-5.69	98	0	1	0	
	92	H-3	-6.43	9	0	90	1	

Table S6. NBO analysis (donor→acceptor) for NMP compounds at BP86/cc-pVTZ level of theory in chloroform. The numbering of the atoms corresponds to Figure 1.

	Donnor NBO (i)	Acceptor NBO (j)	E(2) ^a (kcal mol ⁻¹)	E(j)-E(i) ^b (a.u.)	F(i,j) ^c (a.u.)
NMP-4	π (C9-C13)	π^* (O1-C2)	11.10	0.29	0.051
	π (C9-C13)	π^* (C10-C11)	15.70	0.23	0.054
	π (C10-C11)	π^* (C9-C13)	13.00	0.23	0.050
	LP (O1)	π^* (C2-N3)	20.28	0.59	0.099
	LP (O1)	π^* (C2-C9)	16.61	0.55	0.087
	LP (N3)	π^* (O1-C2)	25.75	0.28	0.077
	LP (N17)	π^* (C16-C21)	38.69	0.22	0.084
	LP (O27)	π^* (C20-C19)	27.36	0.26	0.081
	π^* (C9-C13)	π^* (O1-C2)	23.28	0.06	0.056
	π^* (O1-C2)	π^* (O1-C2)	23.91	0.36	0.190
NMP-7	π (C9-C13)	π^* (O1-C2)	11.61	0.29	0.052
	π (C9-C13)	π^* (C10-C11)	15.81	0.23	0.054
	π (C10-C11)	π^* (C9-C13)	12.73	0.23	0.050
	π (C15-C18)	π^* (C16-C21)	16.02	0.22	0.054
	LP (O1)	π^* (C2-N3)	20.24	0.59	0.099
	LP (O1)	π^* (C2-C9)	16.59	0.55	0.087
	LP (N3)	π^* (O1-C2)	26.51	0.28	0.078
	π^* (O1-C2)	π^* (O1-C2)	24.22	0.36	0.190
	π^* (C12-N17)	π^* (C10-C11)	83.57	0.05	0.077
	π^* (C9-C13)	π^* (O1-C2)	23.42	0.06	0.058
NMP-181	π (C9-C13)	π^* (O1-C2)	23.59	0.2	0.061
	π (C9-C13)	π^* (C10-C11)	16.61	0.23	0.055
	π (C10-C11)	π^* (C9-C13)	11.98	0.23	0.048
	π (C14-C12)	π^* (C15-C16)	16.23	0.22	0.054
	LP (O1)	π^* (C2-O3)	28.07	0.51	0.108
	LP (O1)	π^* (C2-C9)	16.45	0.58	0.089
	LP (O3)	π^* (O1-C2)	40.21	0.25	0.091
	LP (N17)	π^* (C14-C12)	33.81	0.22	0.079
	LP (N6)	σ^* (C8-H53)	6.99	0.55	0.056
	π^* (O1-C2)	π^* (C9-C13)	62.65	0.03	0.065

^a E(2) is the stabilizing energy

^b E(j)-E(i) es the energy difference between NBO donor (i) and acceptor (j) orbitals

^c F(i,j) are the Fock matrix elements between NBO donor (i) and acceptor (j) orbitals

Table S7. Fukui functions, $f^+(r)$ and $f^-(r)$, dual descriptor, $f^{(2)}(r)$, and Parr functions, $P^-(r)$ and $P^+(r)$, for the NMP compounds at BP86/cc-pVTZ level of theory in chloroform.

		$f^+(r)$	$f^-(r)$	$f^{(2)}(r)$	$P^+(r)$	$P^-(r)$
NMP-4	O1	0.063	0.023	0.040	0.104	0.003
	C9	0.049	0.029	0.020	0.107	0.017
	C10	0.041	0.063	-0.022	0.034	0.097
	C11	0.037	0.064	-0.026	0.033	0.089
	C13	0.025	0.070	-0.045	-0.006	0.157
	C14	0.043	0.044	-0.002	0.084	0.088
	N17	0.050	0.011	0.038	0.129	0.001
	C20	0.040	0.053	-0.013	0.055	0.095
	C21	0.072	0.052	0.020	0.146	0.055
	O27	0.048	0.027	0.021	0.079	0.022
NMP-7	O1	0.060	0.025	0.035	0.089	0.006
	C9	0.054	0.031	0.022	0.117	0.020
	C10	0.031	0.061	-0.030	-0.007	0.092
	C11	0.049	0.064	-0.015	0.074	0.088
	C13	0.035	0.073	-0.037	0.029	0.167
	N17	0.072	0.012	0.060	0.205	0.003
	C18	0.046	0.067	-0.022	0.045	0.121
	C19	0.062	0.041	0.021	0.093	0.009
	C20	0.036	0.074	-0.038	-0.002	0.122
	C21	0.055	0.059	-0.004	0.095	0.072
NMP-181	O1	0.028	0.061	-0.033	0.018	0.059
	C2	0.014	0.048	-0.034	0.006	0.077
	N6	0.086	0.002	0.085	0.204	0.000
	C11	0.039	0.057	-0.018	0.066	0.061
	C13	0.024	0.100	-0.076	0.015	0.248
	N17	0.054	0.014	0.041	0.157	0.003
	C18	0.033	0.051	-0.018	0.028	0.078
	C19	0.050	0.036	0.014	0.084	0.008
	C20	0.027	0.064	-0.037	-0.004	0.097
	C21	0.042	0.044	-0.002	0.074	0.040

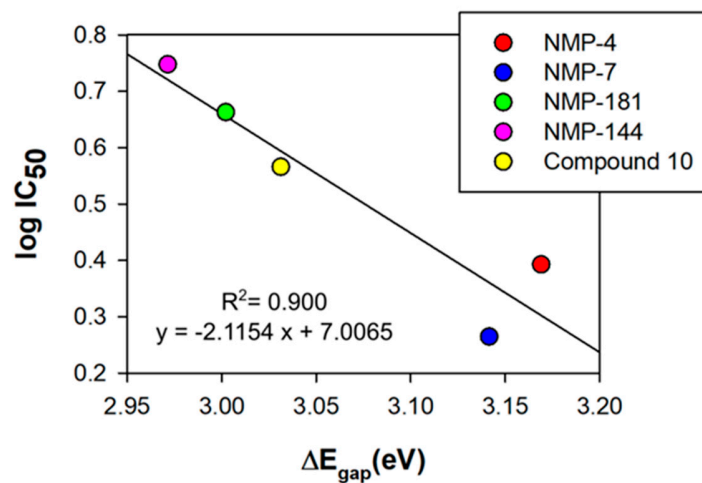


Figure S1. Correlation graph ΔE_{gap} values (in eV) with the experimental logIC₅₀ values (in μM) for the NMP compounds obtained at BP86/cc-pVTZ level of theory in chloroform solvent.

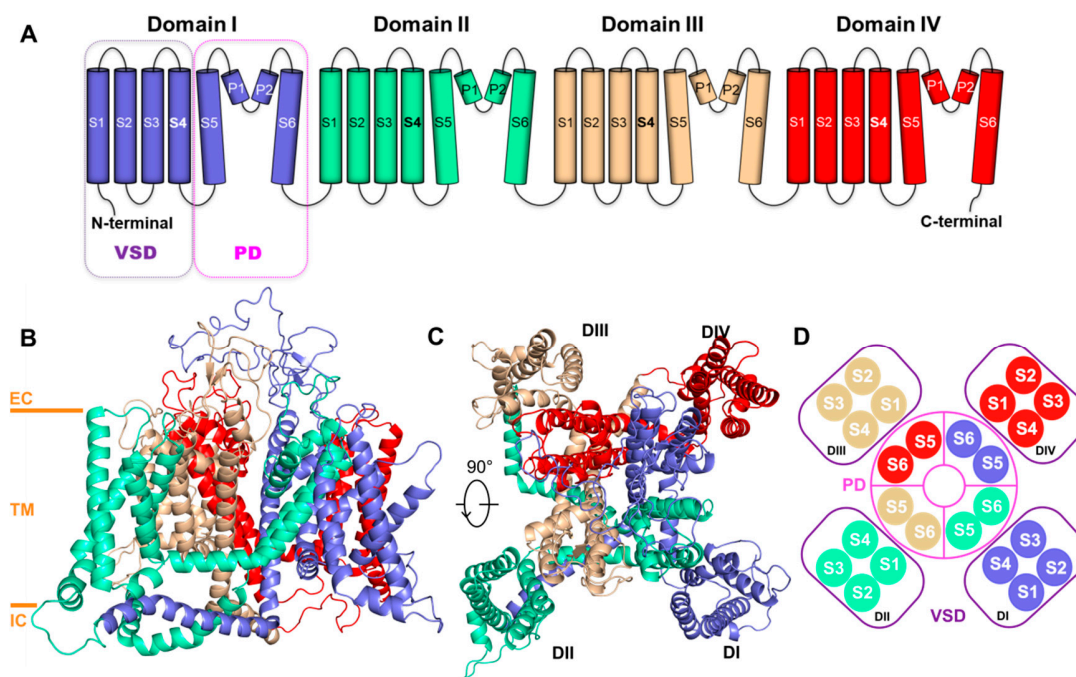


Figure S2. (A) Diagram of the structure Cav3.2 channel, in color code represented the four domains: the Domain I (DI) in blue, the Domain II (DII) in green, the Domain III (DIII) in beige, and the Domain IV (DIV) in red. Each domain contains six transmembrane segments (S1-S6). The segments S1-S4 form the voltage-sensing domain (VSD) and the segments S5-S6 with the segment P (P1 and P2) form the pore domain (PD). (B) Lateral view of the human Cav3.2 channel generated by homology modeling, the extracellular (EC), transmembrane (TM) and intracellular (IC) portion are indicated. (C) Extracellular view of the human Cav3.2 channel. (D) Extracellular view diagram of the spatial distribution of the transmembrane segments of the human Cav3.2 channel.