

Supporting Information
for
Computational-Assisted Development of
Molecularly Imprinted Polymers for Synthetic
Cannabinoid Recognition

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



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The pK_a value, the acid dissociation equilibrium constant, can be obtained from Equation 1, where R is the gas constant, T is the temperature, and $G_{sol}(A^-)$, $G_{sol}(HA)$, and $G_{sol}(H^+)$ represent the Gibbs energies of the conjugate base (A^-), the acid (HA), and the proton in solution (H^+), respectively.

$$pK_{a_{calc}} = \frac{\Delta G_R}{\ln 10 \times RT} = \frac{G_{sol}(H^+) - G_{sol}(HA) + G_{sol}(A^-)}{\ln 10 \times RT}$$

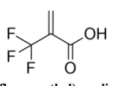

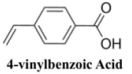

Computationally, we obtained the values for $G_{sol}(A^-)$ and $G_{sol}(HA)$ from geometry optimization calculations followed by natural frequency analysis, for the ionic and neutral forms of the acid, respectively. For more accurate results, geometry optimization was performed with the SMD solvent model for water, including the presence of two explicit water molecules, at the theoretical level ω B97XD, the same as used throughout the study, with a large basis set, aug-cc-TZVP, as indicated in the literature,¹ Table S1. The value of $G_{sol}(H^+)$ is very difficult to obtain computationally; therefore, it is common to parameterize it according to the functional applied. In this study, we will use the 274.7 kcal/mol value obtained by Custodio et al.¹

Table S1: Values of $G_{sol}(A^-)$ and $G_{sol}(HA)$ for each monomer studied in Hartree, as well as the difference between these values in kcal/mol, calculated by $\Delta G_{sol} = [G_{sol}(HA) - G_{sol}(A^-)] \times 627.5$

	G_{sol}(HA) hartree	G_{sol}(A⁻) hartree	Δ G_{sol} kcal/mol
 2-(trifluoromethyl)acrylic Acid	-757.115	-756.671	278.53
 Acrylic Acid	-420.031	-419.583	281.53
 4-vinylbenzoic Acid	-651.012	-650.563	281.82
 Methacrylic Acid	-459.325	-458.876	281.97

The calculated values were very close to the experimental values, Table S2. In addition to differing by no more than 1 pKa unit, the values maintain the same order of magnitude. This result demonstrates that the acidity of each monomer studied was adequately modeled.

Table S2: Experimental and theoretical pK_a values obtained for the monomers studied in this work. The calculated values at the theoretical level ω B97XD/aug-cc-TZVP/SMD(water) in the presence of two explicit water molecules.

	pK_a Exp.	pK_a Calc.	Δ pK_a
 2-(trifluoromethyl)acrylic Acid	2.70 ^a	2.81	0.11
 Acrylic Acid	4.20 ^a	5.02	0.82
 4-vinylbenzoic Acid	4.29 ^b	5.23	0.94
 Methacrylic Acid	4.66 ^a	5.33	0.67

^a From Ref.² ^b From Ref.³

Table S3: Solvation energy values, obtained using the SMD model, for SCs and aprotic solvents.

Synthetic Cannabinoids	Solvents					
	Ace	ACN	Chl	DCM	EtOEt	DMSO
1	-24,77	-24,28	-21,84	-24,43	-21,34	-20,82
2	-24,1	-23,66	-21,05	-23,65	-20,62	-20,46
3	-19,47	-18,85	-17,7	-19,63	-17,41	-15,37
4	-18,21	-17,52	-16,7	-18,38	-16,53	-14,32
5	-21,51	-21,08	-19,17	-21,33	-18,56	-17,88
6	-20,34	-19,98	-18,42	-20,49	-17,65	-16,41
7	-21,08	-20,75	-19,27	-21,45	-18,46	-16,86

Table S4: Molecular structures of compounds 1 to 5 and their electrostatic potential surfaces.

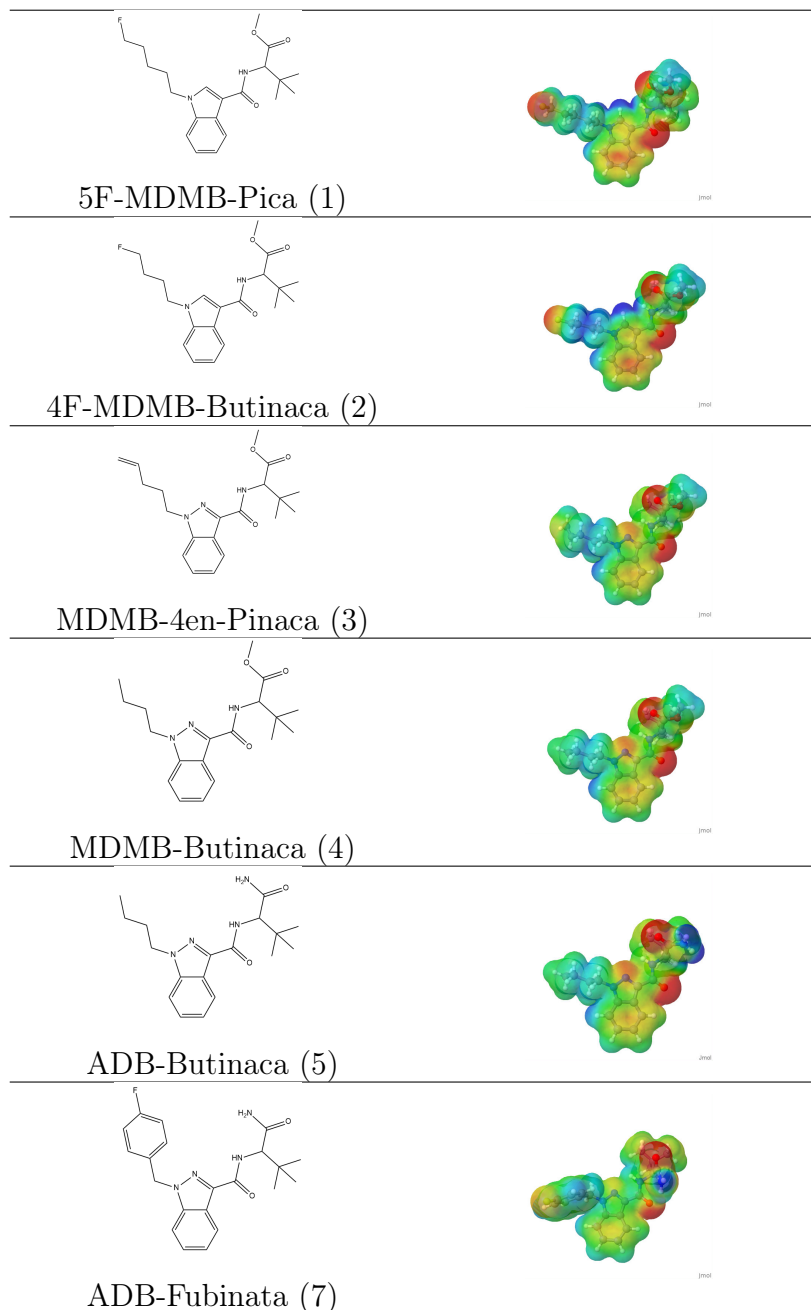


Table S5: Complexation energy values, obtained for SCs and FMs

Synthetic Cannabinoids	Acids			
	Acrylic	Metacrylic	2(trifluoromethyl) acrylic	4-vinylbenzoic
1	-40,81	-37,84	-47,23	-44,91
2	-38,22	-41,11	-44,06	-40,29
3	-26,04	-27,34	-27	-30,45
4	-26,84	-24,6	-27,96	-30,84
5	-34,86	-35,79	-37,68	-38,2
6	-37,37	-38,23	-39,85	-40,86
7	-39,58	-40,18	-41,55	-46,42

Table S6: Interactions between all synthetic cannabinoids and functional monomers obtained using the Binana software.



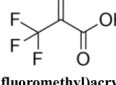
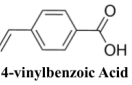
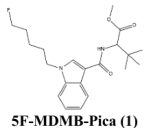
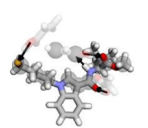
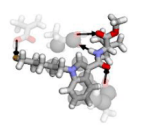
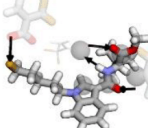
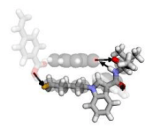
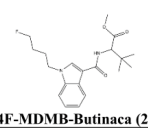
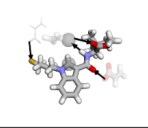
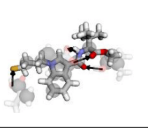
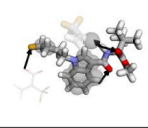
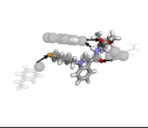
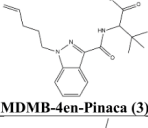
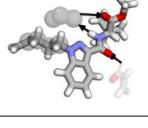
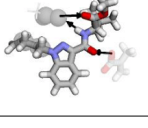
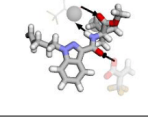
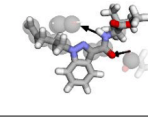
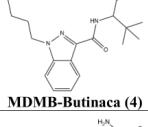
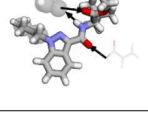
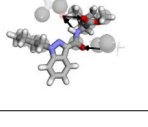
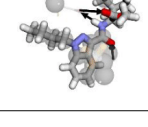
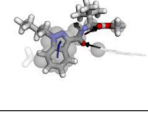
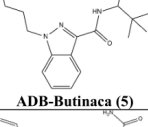
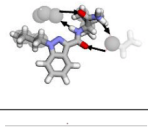
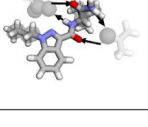
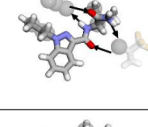
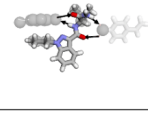
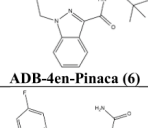
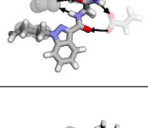
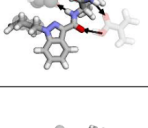
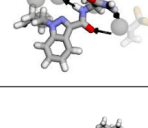
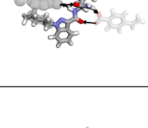
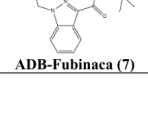
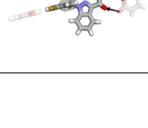
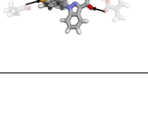
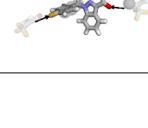
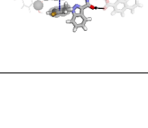
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 5F-MDMB-Pica (1)				
 4F-MDMB-Butinaca (2)				
 MDMB-4en-Pinaca (3)				
 MDMB-Butinaca (4)				
 ADB-Butinaca (5)				
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 ADB-Fubinaca (7)				

Table S7: Interactions between all synthetic cannabinoids and explicit solvent molecules obtained using the Binana software

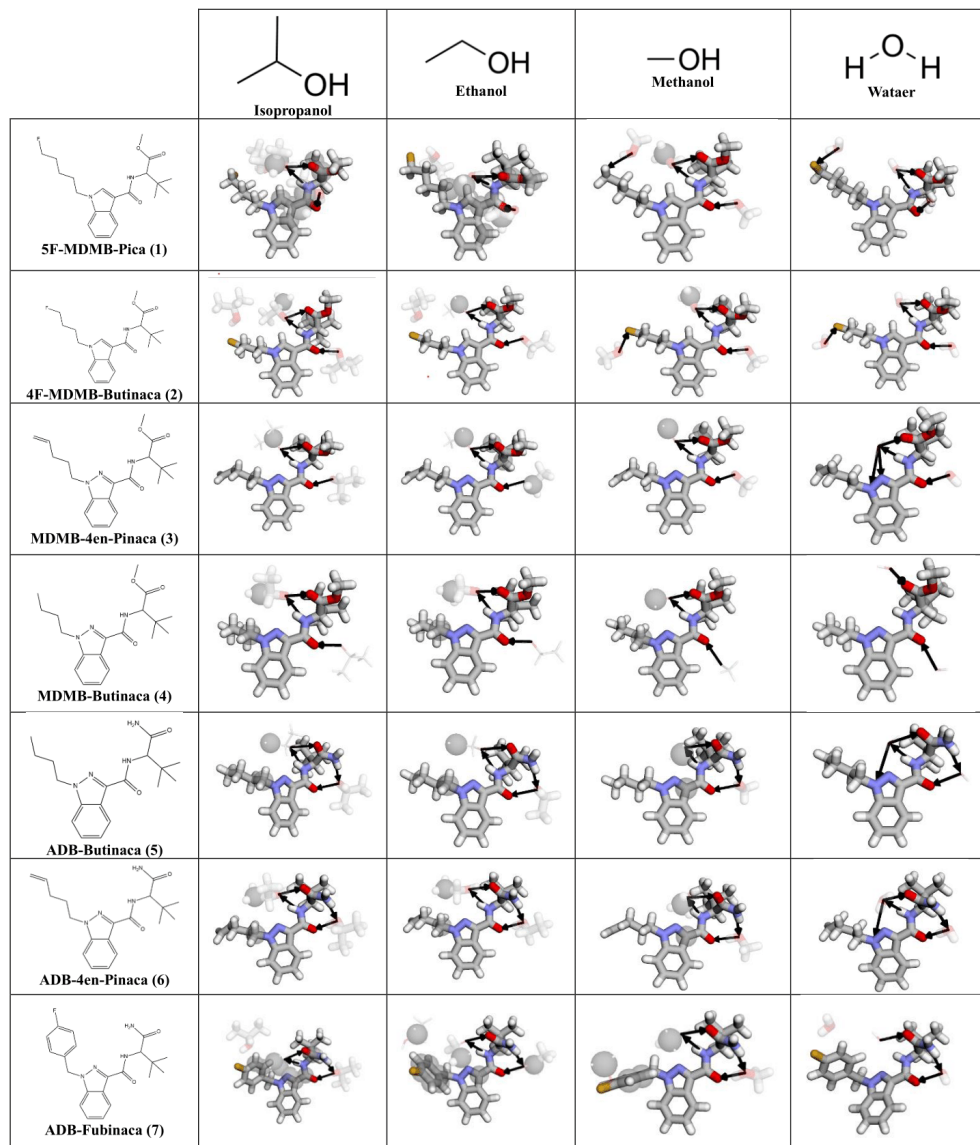


Table S8: Solvation energy values, obtained using explicit molecules protic solvents

Synthetic Cannabinoids	Solvents			
	i-PrOH	EtOH	MeOH	H2O
1	-34,37	-30,43	-32,84	-25,82
2	-31,67	-31,66	-32,67	-28,24
3	-21,15	-21,04	-20,45	-20,83
4	-21,89	-21,59	-21,45	-15,1
5	-29,11	-28,8	-30,94	-26,59
6	-31,58	-31,1	-32,62	-29,06
7	-35,38	-36,31	-36,02	-29,57

References

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