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Informações Suplementares

Molecular Dynamics Simulations of Omega-3 and Omega-6 Lipid Mediators as Partial Agonists of PPARγ

Simulações de Dinâmica Molecular de Mediadores Lipídicos Ômega-3 e Ômega-6 como Agonistas Parciais do PPARγ

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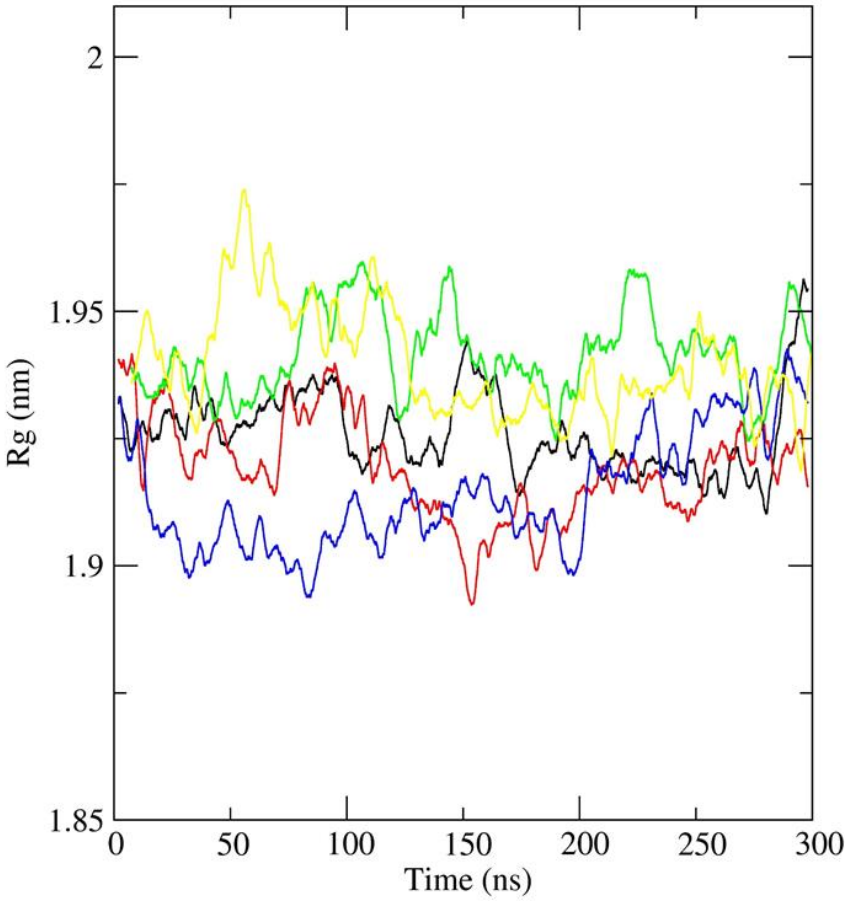
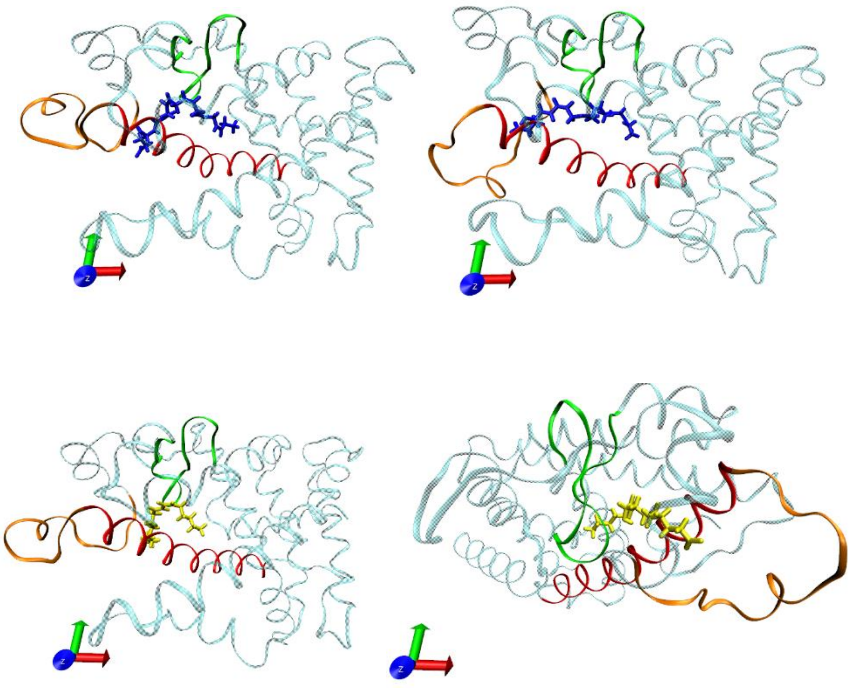


Figure S1. Radius of gyration (RG) analysis of apo-PPAR γ and PPARγ-ligand complexes (average of the 3 replicas).



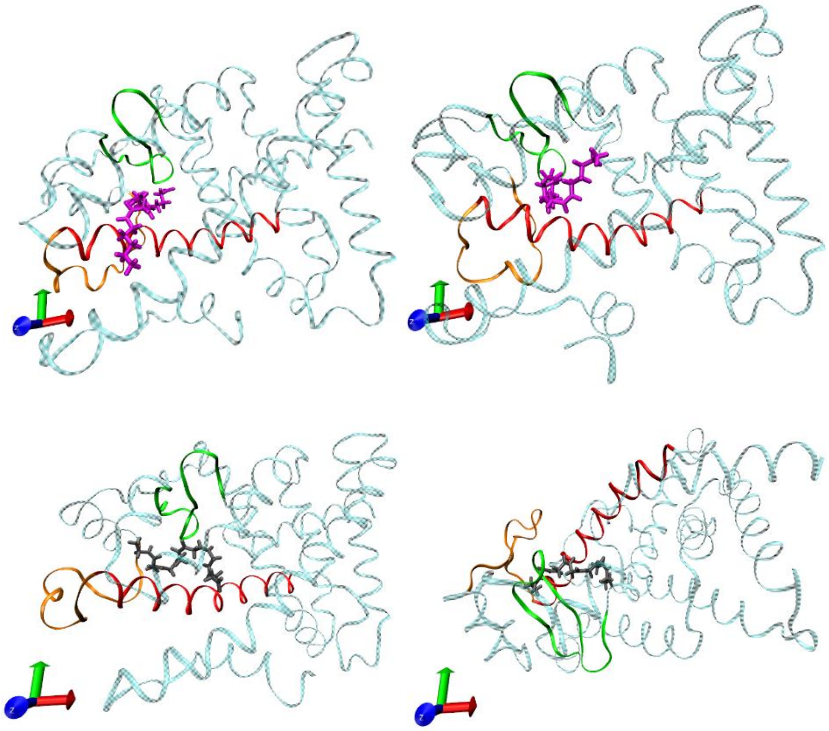


Figure S2. *Snapshots of the initial and final states of the simulations.* On the left are the frames at the initial time, and on the right are the frames at the final time of the simulations. The ligand is shown in licorice representation, with secondary structure elements of the protein colored as follows: helix 3 in red, the loop in orange, and beta sheets in green. The ligands are colored according to the molecule they represent: blue for 4HDHA, yellow for 9HODE, purple for arachidonic acid, and gray for DHA.

Table S1. Ligands' top 10 docking poses ranked by the total energy, which is composed of the torsional energy of the ligand (not shown) and the intermolecular and intramolecular interactions according to the electrostatic and vdW potentials.

Pose	Total Energy	Interaction Energy	vdW	Coul
9HODE-1	-36.302	-54.113	-21.242	-32.871
9HODE-2	-34.843	-55.258	-19.212	-36.046
9HODE-3	-34.660	-53.362	-19.082	-34.280
9HODE-4	-34.426	-53.101	-19.268	-33.833
9HODE-5	-33.974	-54.711	-23.566	-31.145
AA-1	-32.712	-54.517	-22.343	-32.174
9HODE-6	-31.437	-51.238	-18.395	-32.843
AA-2	-31.401	-54.281	-26.721	-27.560
AA-3	-30.236	-54.764	-17.559	-37.205
4HDHA-1	-30.228	-57.966	-27.571	-30.395

AA-4	-30.208	-54.717	-23.745	-30.972
AA-5	-30.189	-52.359	-9.816	-42.543
AA-6	-29.691	-52.182	-11.590	-40.592
AA-7	-29.423	-52.215	-17.513	-34.702
4HDHA-2	-29.330	-59.440	-29.561	-29.879
AA-8	-29.023	-52.647	-14.579	-38.068
4HDHA-3	-28.986	-57.550	-25.617	-31.933
AA-9	-28.891	-53.256	-20.461	-32.795
DHA-1	-28.775	-55.384	-25.753	-29.631
AA-10	-28.609	-53.366	-16.956	-36.410
DHA-2	-28.592	-56.794	-19.769	-37.025
4HDHA-4	-28.532	-53.968	-21.126	-32.842
4HDHA-5	-28.419	-55.397	-25.128	-30.269
9HODE-7	-28.333	-52.658	-20.591	-32.067
4HDHA-6	-28.155	-54.269	-19.601	-34.668
9HODE-8	-27.861	-50.385	-15.043	-35.342
DHA-3	-27.790	-53.527	-24.465	-29.062
4HDHA-7	-27.683	-57.594	-22.835	-34.759
4HDHA-8	-27.569	-58.888	-29.482	-29.406
4HDHA-9	-27.545	-60.650	-25.592	-35.058
4HDHA-10	-27.345	-54.149	-23.172	-30.977
DHA-4	-26.992	-53.050	-23.058	-29.992
9HODE-9	-26.626	-46.415	-18.349	-28.066
DHA-5	-26.489	-52.660	-23.973	-28.687
9HODE-10	-26.234	-53.198	-19.117	-34.081
DHA-6	-25.978	-53.774	-24.057	-29.717
DHA-7	-25.676	-55.281	-16.105	-39.176
DHA-8	-25.428	-54.799	-24.364	-30.435
DHA-9	-25.350	-53.862	-22.281	-31.581
DHA-10	-24.794	-51.309	-21.514	-29.795

Table S2. Root mean square deviation (RMSD) values of apo-PPAR γ and PPARγ-ligand complexes.

		Simulation time (ns)	**RMSD value per replica (nm)**	**RMSD (replicas average) (nm)**
Apo	-	500	0.25	0.25

	r1	500	0.26	
AA	r2	500	0.27	0.26
	r3	500	0.23	
	r1	300	0.25	
DHA	r2	300	0.26	0.26
	r3	300	0.27	
	r1	500	0.26	
4HDHA	r2	500	0.24	0.24
	r3	500	0.24	
	r1	300	0.27	
9HODE	r2	300	0.29	0.28
	r3	300	0.27	

Table S3. Hydrogen bond frequencies in the protein-ligand complexes simulations, according to VMD and AMBER calculations.

Ligand	Simulation Replica	Residues	Hydrogen Bonds	
			VMD Frequency	AMBER Frequency
AA[a]	r1	K265	0.23	0.25
		R288	0.15	0.16
		S342	0.49	0.59
		E343	0.11	-
	r2	R288	0.48	0.50
		S342	0.34	0.48
	r3	R288	0.38	0.38
		S342	0.77	0.86
DHA[b]	r1	Y327	0.86	0.92
		K367	0.68	0.83
	r2	Y327	0.77	0.82
		K367	0.73	0.89
	r3	Y327	0.58	0.63
		K367	0.56	0.72
4HDHA[c]	r1	H266	0.43	0.32
		R280	0.93	0.95
	r2	K265	0.10	-
		H266	0.48	0.48
		R280	0.91	0.96
	r3	K265	0.56	0.43
		S342	0.82	0.88
		E343	0.11	-
9HODE[d]	r1	K265	0.32	0.36
		R280	0.29	0.30
		S342	0.60	0.57
	r2	K263	0.21	-
		K265	-	0.26
		R280	0.62	0.68
		S342	-	0.14
	r3	R280	0.83	0.88
		S342	0.14	0.20

[a]Arachidonic acid; [b]docosahexaenoic acid; [c]4-hydroxydocosahexaenoic acid; [d]9-hydroxyoctadecadienoic acid. Minor differences observed in the residues list and frequencies values are attributed to the distinct donor–acceptor (D–A) distance and angles cut-offs used as pattern by each tool. VMD uses a D–A distance and a hydrogen–donor–acceptor (H–D–A) angle cut-off of 3.5 Å and 30°, respectively, whereas AMBER uses a D–A distance and a donor–hydrogen–acceptor (D–H–A) angle cut-off of 3.0 Å and 135°, respectively.

Table S4. Positively charged residues that showed binding energy ≤ -1 kcal.mol^{-1} from MMPBSA calculations in at least one simulation replica. Energy values ≤ -4.5 kcal.mol^{-1} are highlighted.

Res	AA			DHA			4HDHA			9HODE		
	r1	r2	r3	r1	r2	r3	r1	r2	r3	r1	r2	**r3**
R212	-2.6	-2.5	-2.4	-2.2	-2.2	-2.3	-1.8	-1.8	-2.3	-2.3	-1.8	**-1.9**
K216	-2.7	-2.7	-2.6	-2.3	-2.3	-2.3	-2.0	-2.1	-2.8	-2.5	-2.0	**-2.2**
K224	-3.6	-3.4	-3.4	-2.7	-2.7	-2.7	-2.5	-2.6	-3.6	-3.2	-2.5	**-2.8**
K230	-4.1	-4.3	-4.0	-3.3	-4.1	-3.2	-2.9	-2.9	0.0	-3.6	-2.8	**-3.1**
K232	**-4.8**	**-5.0**	**-4.7**	-3.1	-3.0	-3.1	-3.2	-3.5	**-5.1**	-4.4	-3.3	**-3.6**
R234	-4.0	-4.0	-3.6	-3.1	-3.5	-3.3	-2.8	-2.9	-3.7	-3.5	-2.7	**-3.0**
K240	-3.2	-3.5	-3.1	-2.5	-2.7	-2.6	-2.5	-2.6	-3.3	-3.1	-2.5	**-2.7**
244	-4.2	-3.7	-4.0	-2.5	-2.5	-2.6	-3.6	-3.7	-4.2	-4.3	-3.8	**-4.0**
K261	-4.0	-4.0	-4.0	-2.9	-2.9	-2.9	**-4.8**	**-4.5**	-4.0	**-4.6**	**-4.9**	**-4.3**
K263	**-5.3**	**-5.5**	**-4.8**	-3.1	-3.0	-3.0	**-4.9**	**-5.5**	**-4.9**	**-6.0**	**-5.5**	**-5.7**
K265	**-5.6**	**-4.8**	**-5.6**	-3.5	-3.3	-4.0	**-5.5**	**-5.7**	**-4.9**	**-4.6**	**-5.3**	**-5.4**
K275	-3.4	-3.5	-3.9	-3.6	-3.6	-3.7	**-5.2**	**-4.6**	-3.5	-3.7	**-6.4**	**-4.4**
R280	-4.2	-4.4	**-4.6**	-3.5	-3.8	-4.1	-4.3	**-5.7**	-3.9	**-4.8**	**-4.7**	**-4.3**

R288	**-7.7**	**-6.6**	**-7.2**	**-5.9**	**-5.9**	**-6.1**	**-4.8**	**-6.2**	**-8.3**	**-7.6**	**-5.1**	**-6.6**
K301	-3.4	-3.4	-3.3	-3.2	-3.3	-3.2	-2.7	-2.8	-3.6	-3.5	-2.7	**-3.0**
K319	-3.1	-2.9	-3.0	-3.7	-3.7	-3.7	-2.7	-2.8	-3.0	-3.0	-2.6	**-2.8**
K336	-3.4	-3.4	-3.5	-3.3	-3.3	-3.3	-2.8	-3.0	-3.5	-3.3	-2.8	**-3.0**
R350	-3.6	-3.3	-3.5	-3.7	-3.9	-3.7	-3.1	-3.2	-3.4	-3.4	-3.0	**-3.2**
K354	-3.4	-3.2	-3.5	-3.9	-4.0	-3.8	0.0	-3.3	-3.3	-3.4	-3.2	**-3.3**
R357	-3.4	-3.3	-3.6	-3.8	-3.8	-3.7	-4.2	-4.0	-3.2	-3.5	-4.1	**-3.9**
K358	-3.0	-2.9	-3.1	-4.3	-4.2	-4.2	-3.3	-3.2	-2.9	-3.0	-3.0	**-3.1**
K367	-3.8	-3.5	-3.9	**-4.6**	**-5.5**	-4.4	-3.3	-3.5	-3.7	-3.8	-3.2	**-2.8**
K373	-3.1	-3.0	-3.1	-3.8	-3.8	-3.7	-2.5	-2.6	-2.9	-2.9	-2.4	**-2.6**
R397	-3.4	-3.2	-3.2	-4.0	-4.1	-4.0	-2.5	-2.6	-3.0	-2.9	-2.5	**-2.7**
K404	-2.1	-2.1	-2.0	-2.4	-2.4	-2.4	-1.7	-1.7	-1.9	-1.9	-1.6	**-1.7**
K422	-2.3	-2.2	-2.2	-2.2	-2.3	-2.3	-1.7	-1.7	0.0	0.0	0.0	**-1.8**
K434	-2.7	-2.6	-2.6	-2.9	-2.9	-2.9	-2.0	-2.1	-2.4	-2.3	-1.9	**-2.1**
K438	-3.2	-3.1	-3.0	-3.4	-3.5	-3.4	-2.4	-2.5	-2.8	-2.7	-2.3	**-2.5**
R443	-3.1	-3.0	-2.9	-3.7	-3.7	-3.7	-2.4	-2.4	-2.8	-2.7	-2.2	**-2.5**

K457	-3.2	-3.4	-3.5	**-5.3**	**-5.1**	**-4.7**	-3.4	-3.4	-3.1	-3.2	-3.2	**-3.3**
K458	-2.8	-2.8	-2.9	-4.1	-4.1	-4.0	-2.9	-2.9	-2.6	-2.7	-2.8	**-2.8**
K474	-2.8	-2.8	-2.9	-3.8	-3.8	-4.0	-2.8	-2.7	-2.8	-2.9	-2.5	**-2.7**

Table S5. Neutral residues that showed total binding energy ≤ -1 kcal.mol^{-1} from MMPBSA calculations in at least one simulation replica. The most favorable energy values from each replica are highlighted.

Res	AA			DHA			4HDHA			9HODE		
	r1	r2	r3	r1	r2	r3	r1	r2	r3	r1	r2	**r3**
F264	-	-	-	**-1.0**	-0.8	0.0	-0.7	-1.2	**-1.6**	-0.4	**-1.1**	**-0.7**
H266	-	-	-	-	-	-	-0.6	**-1.5**	-0.1	-	-	**-**
I281	-	-	-	-1.0	-0.8	**-1.1**	-1.1	-0.7	**-1.9**	-0.4	**-1.0**	**-0.8**
C285	-1.4	-1.3	**-1.7**	**-1.8**	**-1.8**	-1.7	**-1.8**	-1.5	-1.4	**-1.4**	-1.3	**-1.4**
Y327				-0.9	**-1.0**	-0.7						
L330	**-2.0**	-1.6	-1.2	-1.3	**-1.5**	-1.3	**-1.0**	-0.4	-0.8	**-1.6**	-0.8	**-1.3**
I341	-1.0	-1.2	**-1.3**	**-1.4**	-1.3	**-1.4**	-1.5	-1.4	**-1.9**	**-1.6**	-1.3	**-1.3**
M348	-	-	-	-	-	-	**-1.1**	-0.9	-0.9	-	-	**-**
M364	**-1.2**	-0.7	-0.9	-	-	-	-	-	-	-	-	**-**

Table S6. Comparison between vacuum potential energy and total binding energy of some positively charged residues. Residues' polar solvation energy values ≥ 15.0 kcal.mol^{-1} are displayed.

Ligand	Simulation replica	Residues	Per residue MM/PBSA energy values (kcal.mol^{-1})		
			Vacuum energy	Polar solvation energy	Total binding energy
AA	r1	K265	-14.4	-	-5.6
		R288	-14.5	-	-7.7
	r2	K263	-7.2	-	-5.5
		R288	-18.9	-	-6.6
	r3	K265	-10.9	-	-5.6
		R288	-18.3	-	-7.2
DHA	r1	R288	-8.3	-	-5.9
		K367	**-24.5**	19.9	**-4.6**
		K457	-6.5	-	-5.3
	r2	R288	-8.2	-	-5.9
		K367	**-25.0**	19.5	**-5.5**
		K457	-6.4	-	-5.1
	r3	R288	-8.4	-	-6.1
		K367	**-24.1**	19.8	**-4.4**
		K457	-6.2	-	-4.7
4HDHA	r1	K263	-5.6	-	-4.9
		K265	-9.0	-	-5.5
		K275	-6.7	-	-5.2
		R280	**-25.6**	21.5	**-4.3**
		R288	-7.2	-	-4.8
	r2	K263	-6.6	-	-5.5
		K265	-8.7	-	-5.7
		R280	**-23.6**	18.1	**-5.7**
		R288	-9.3	-	-6.2
	r3	K232	-5.8	-	-5.1
		K263	-5.3	-	-4.9
		K265	**-20.2**	15.4	**-4.9**
		R288	-15.5	-	-8.3
9HODE	r1	K263	-11.3	-	-6.0
		K265	-15.1	-	-4.6

		R280	-11.3	-	-4.8
		R288	-14.0	-	-7.6
	r2	K263	-13.0	-	-5.5
		K265	-8.4	-	-5.3
		K275	-9.1	-	-6.4
		R280	**-20.4**	15.9	**-4.7**
	r3	K263	-7.6	-	-5.7
		K265	-7.3	-	-5.4
		R280	**-22.5**	18.3	**-4.3**
		R288	-9.2	-	-6.6