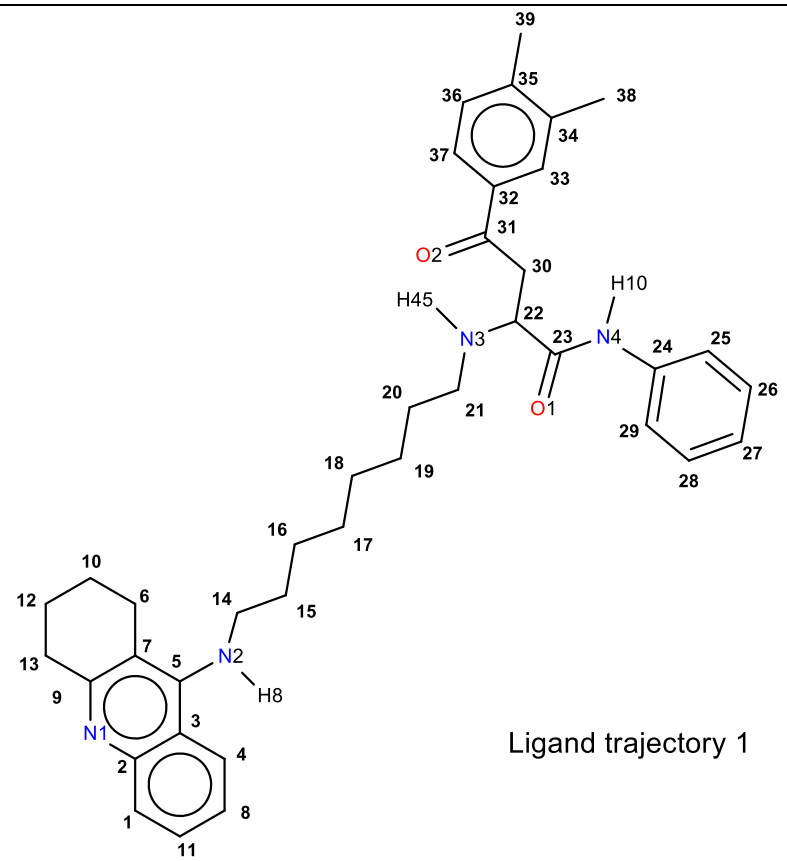
Electronic Supplementary Information

Molecular recognition of acetylcholinesterase and its subnanomolar reversible inhibitor: a molecular simulations study

MajaVitorović-Todorović[1*], Ilija Cvijetić[2], Mire Zloh[3,4] Andrej Perdih[5]

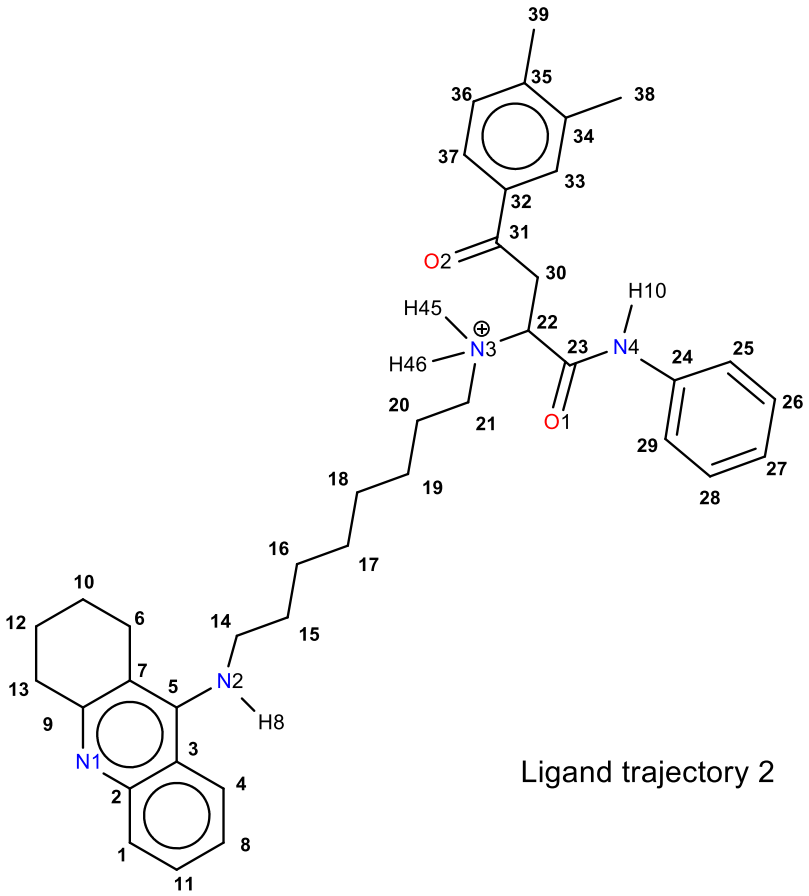
[1]Military Technical Institute; Ratka Resanovića 1, Belgrade, Serbia; mvitod@chem.bg.ac.rs
[2]Innovation Center of the Faculty of Chemistry, University of Belgrade, Serbia; ilija@chem.bg.ac.rs
[3]University Business Academy, Faculty of Pharmacy, Trg Mladenaca 5, Novi Sad, Serbia, zloh@live.co.uk
[4]Nanopuzzle Medicines Design Ltd, Bessemer Road, Stevenage, United Kingdom
[5]National Institute of Chemistry,Hajdrihova 19, 1000 Ljubljana, Slovenia, andrej.perdih@ki.si,
***** Correspondance: mvitod@chem.bg.ac.rs; Tel.: +381-11-3401-255 (M.V.T)

Table S1. The partial atomic charges for the ligand in all six Trajectories.



O1	OG2D1	-0.486	C21	CG321	-0.112
C23	CG2O1	0.446	N1	NG2R60	-0.658
N4	NG2S1	-0.515	C2	CG2R61	0.372
C24	CG2R61	0.139	C3	CG2R61	-0.003
H10	HGP1	0.332	C5	CG2R61	0.078

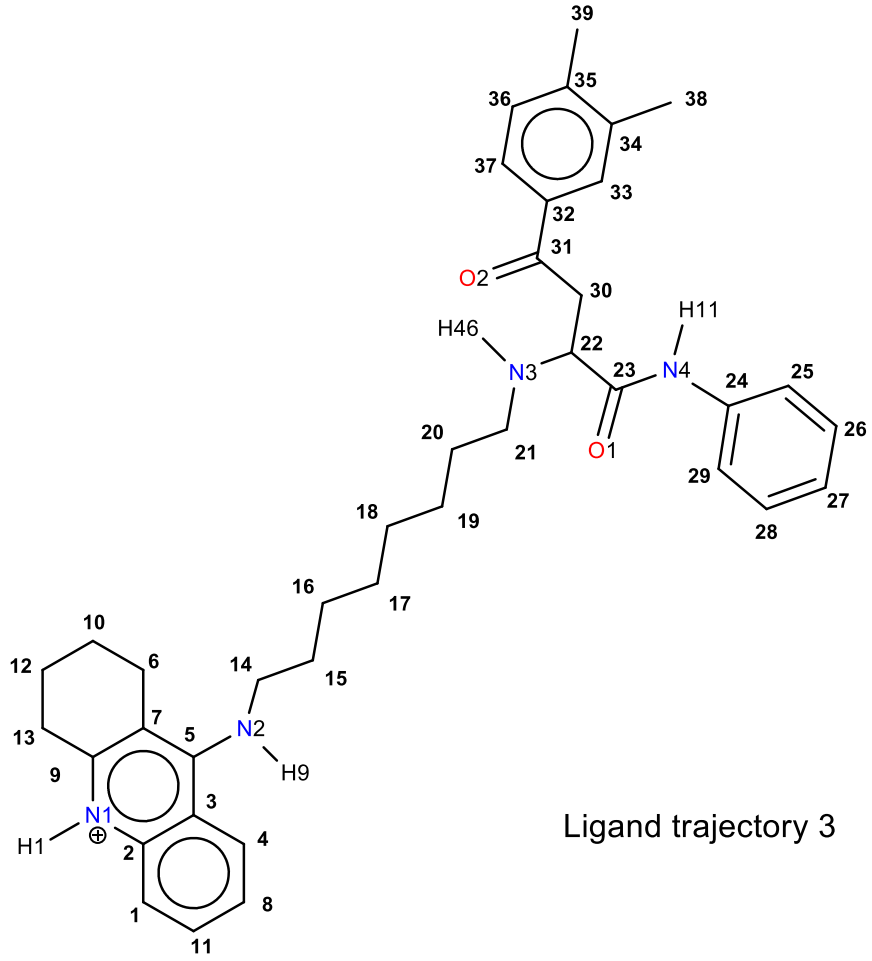
C22	CG311	0.032	C7	CG2R61	-0.021
C30	CG321	-0.161	C9	CG2R61	0.298
C31	CG2O5	0.337	N2	NG311	-0.415
O2	OG2D3	-0.470	H8	HGPAM1	0.338
C32	CG2R61	0.122	C14	CG321	-0.168
N3	NG311	-0.406	C21	CG321	-0.112
H45	HGPAM1	0.300	N1	NG2R60	-0.658



Ligand trajectory 2

O1	OG2D1	-0.490	H46	HGP2	0.320
C23	CG2O1	0.397	C21	CG324	0.175
N4	NG2S1	-0.395	N1	NG2R60	-0.658
C24	CG2R61	0.139	C2	CG2R61	0.372
H10	HGP1	0.318	C3	CG2R61	-0.003
C22	CG314	0.358	C5	CG2R61	0.078
C30	CG321	-0.177	C7	CG2R61	-0.021
C31	CG2O5	0.337	C9	CG2R61	0.298
O2	OG2D3	-0.470	N2	NG311	-0.415

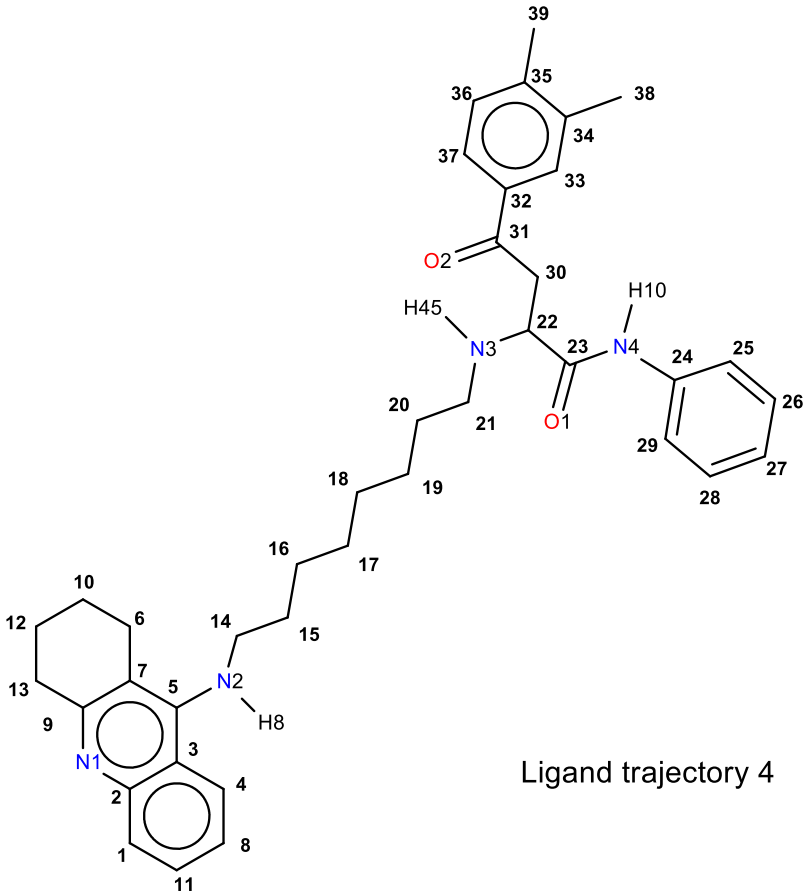
C32	CG2R61	0.122	H8	HGPAM1	0.338
N3	NG3P2	-0.384	C14	CG321	-0.168
H45	HGP2	0.320			



Ligand trajectory 3

O1	OG2D1	-0.486	C21	CG324	-0.112
C23	CG2O1	0.446	N1	NG2R61	-0.070
N4	NG2S1	-0.515	H1	HGP2	0.456
C24	CG2R61	0.139	C2	CG2R61	0.096
H11	HGP1	0.332	C3	CG2R61	0.031
C22	CG311	0.032	C5	CG2R61	0.115
C30	CG321	-0.161	C7	CG2R61	0.088
C31	CG2O5	0.337	C9	CG2R61	0.228

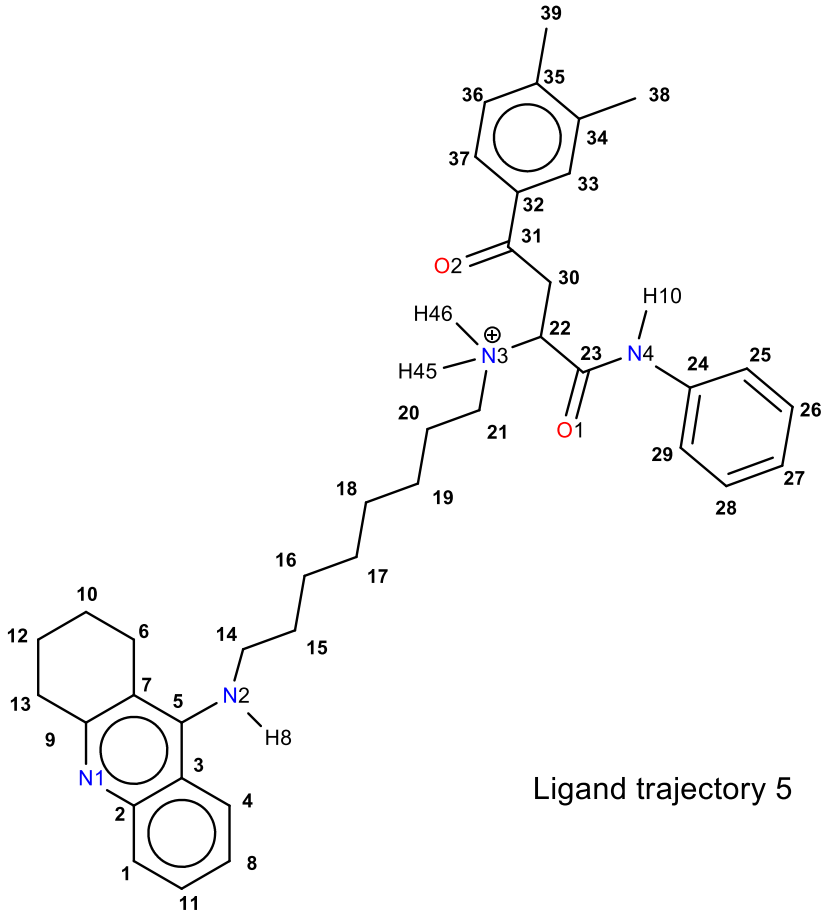
O2	OG2D3	-0.470	N2	NG311	-0.415
C32	CG2R61	0.122	H9	HGPAM1	0.338
N3	NG311	-0.406	C14	CG321	-0.168
H46	HGPAM1	0.300			



Ligand trajectory 4

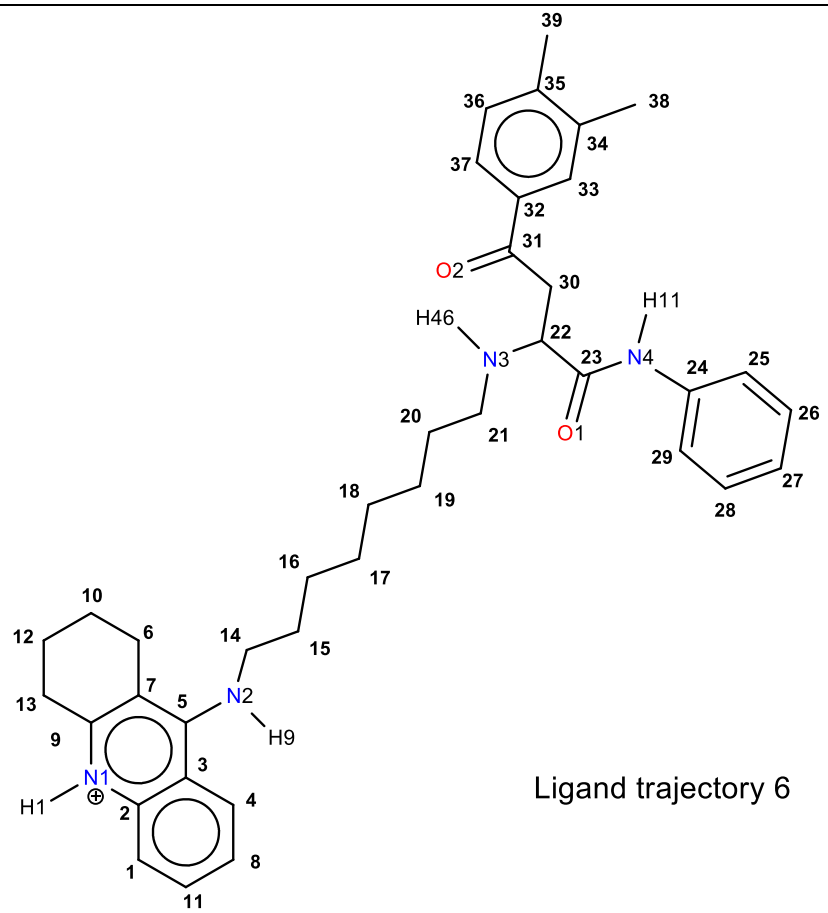
O1	OG2D1	-0.486	H45	HGPAM1	0.300
C23	CG2O1	0.428	C21	CG321	0.002
N4	NG2S1	-0.506	N1	NG2R60	-0.658
C24	CG2R61	0.145	C2	CG2R61	0.328
H10	HGP1	0.331	C3	CG2R61	-0.024
C22	CG311	0.152	C5	CG2R61	0.064
C30	CG321	-0.158	C7	CG2R61	-0.004
C31	CG2O5	0.333	C9	CG2R61	0.349
O2	OG2D3	-0.4700	N2	NG311	-0.548

C32	CG2R61	0.121	H8	HGPAM1	0.338
N3	NG311	-0.647	C14	CG321	-0.034



Ligand trajectory 5

O1	OG2D1	-0.490	H45	HGP2	0.320
C23	CG2O1	0.372	H46	HGP2	0.320
N4	NG2S1	-0.387	C21	CG324	0.189
C24	CG2R61	0.145	N1	NG2R60	-0.658
H10	HGP1	0.318	C2	CG2R61	0.349
C22	CG314	0.408	C3	CG2R61	-0.004
C30	CG321	-0.196	C5	CG2R61	0.064
C31	CG2O5	0.353	C7	CG2R61	-0.024
O2	OG2D3	-0.470	C9	CG2R61	0.328
C32	CG2R61	0.121	N2	NG311	-0.548
N3	NG3P2	-0.373	H8	HGPAM1	0.338
			C14	CG321	-0.034



Ligand trajectory 6

O1	OG2D1	-0.486	C21	CG324	-0.112
C23	CG2O1	0.428	N1	NG2R61	-0.058
N4	NG2S1	-0.506	H1	HGP2	0.414
C24	CG2R61	0.145	C2	CG2R61	0.298
H11	HGP1	0.332	C3	CG2R61	0.124
C22	CG311	0.152	C5	CG2R62	0.075
C30	CG321	-0.158	C7	CG2R61	0.029
C31	CG2O5	0.333	C9	CG2R62	0.031
O2	OG2D3	-0.470	N2	NG311	-0.548
C32	CG2R61	0.121	H9	HGPAM1	0.338
N3	NG311	-0.548	C14	CG321	0.075
H46	HGPAM1	0.338			

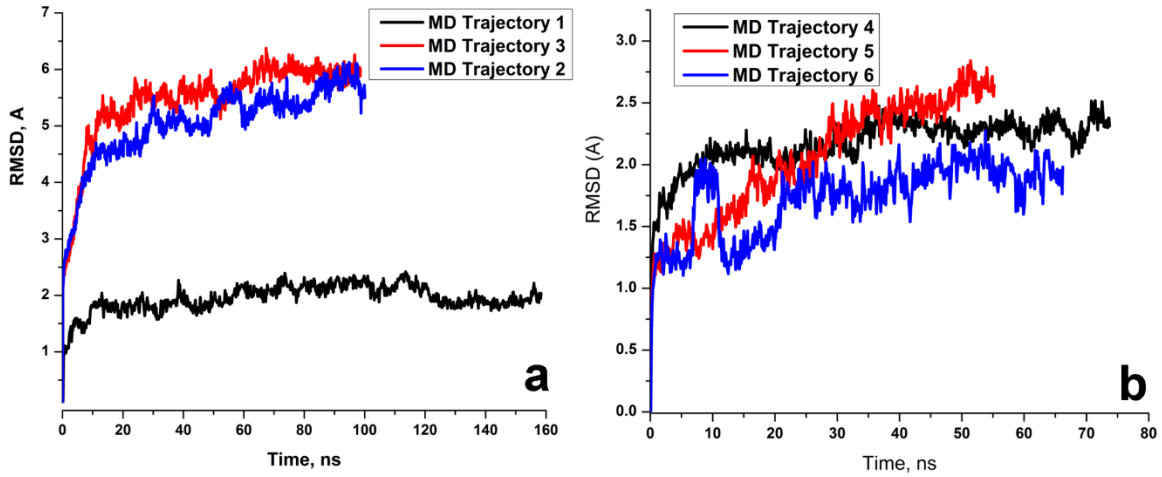


Figure S2. The Root Mean Square Deviation (RMSD) for the MD trajectories 1-3 (a) and Trajectories 4-6 (b).

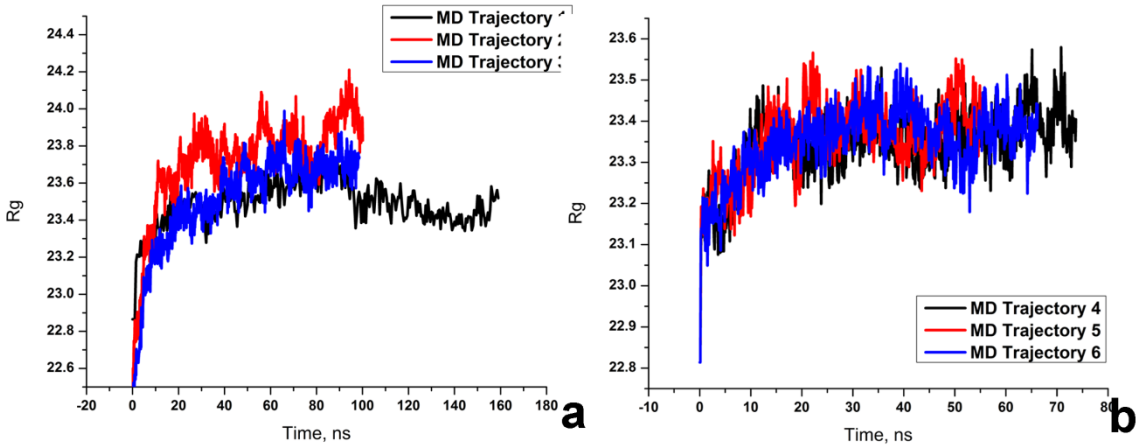


Figure S3. Radius of gyration (Rg) for the MD trajectories 1-3 (a) and Trajectories 4-6 (b).

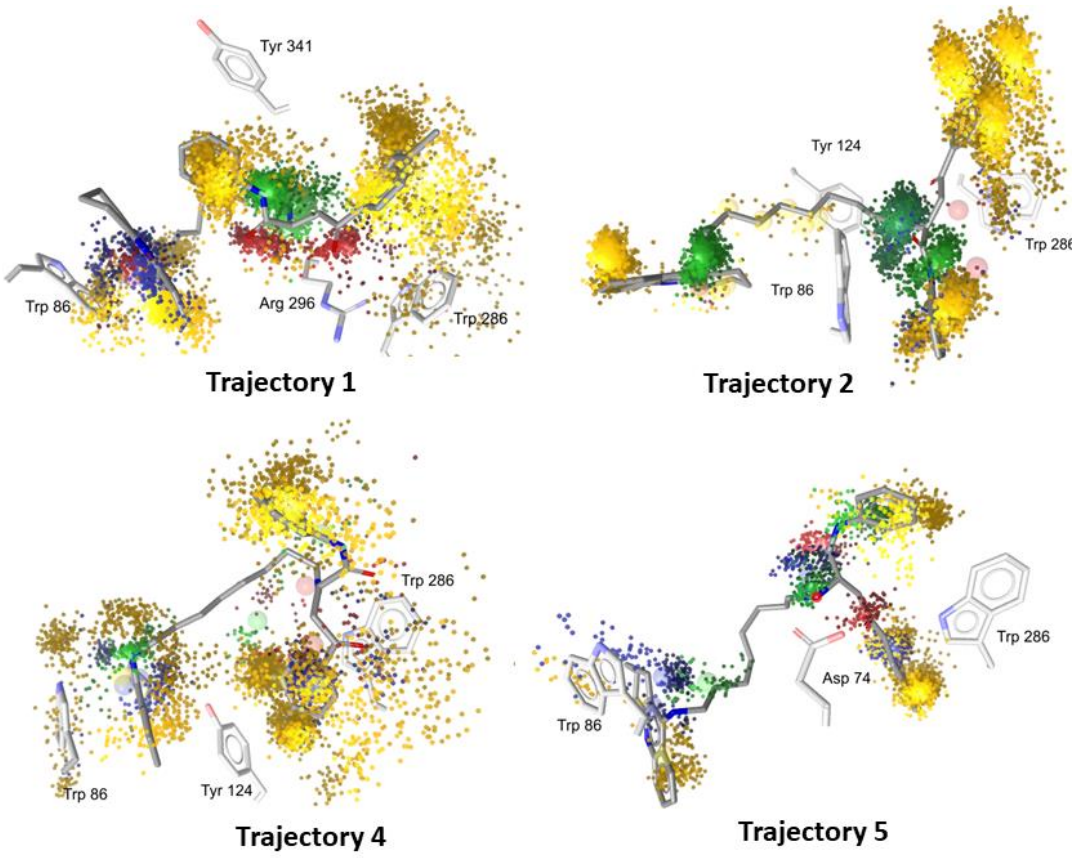


Figure S4. 3D representation of the dynophores for the selected MD trajectories

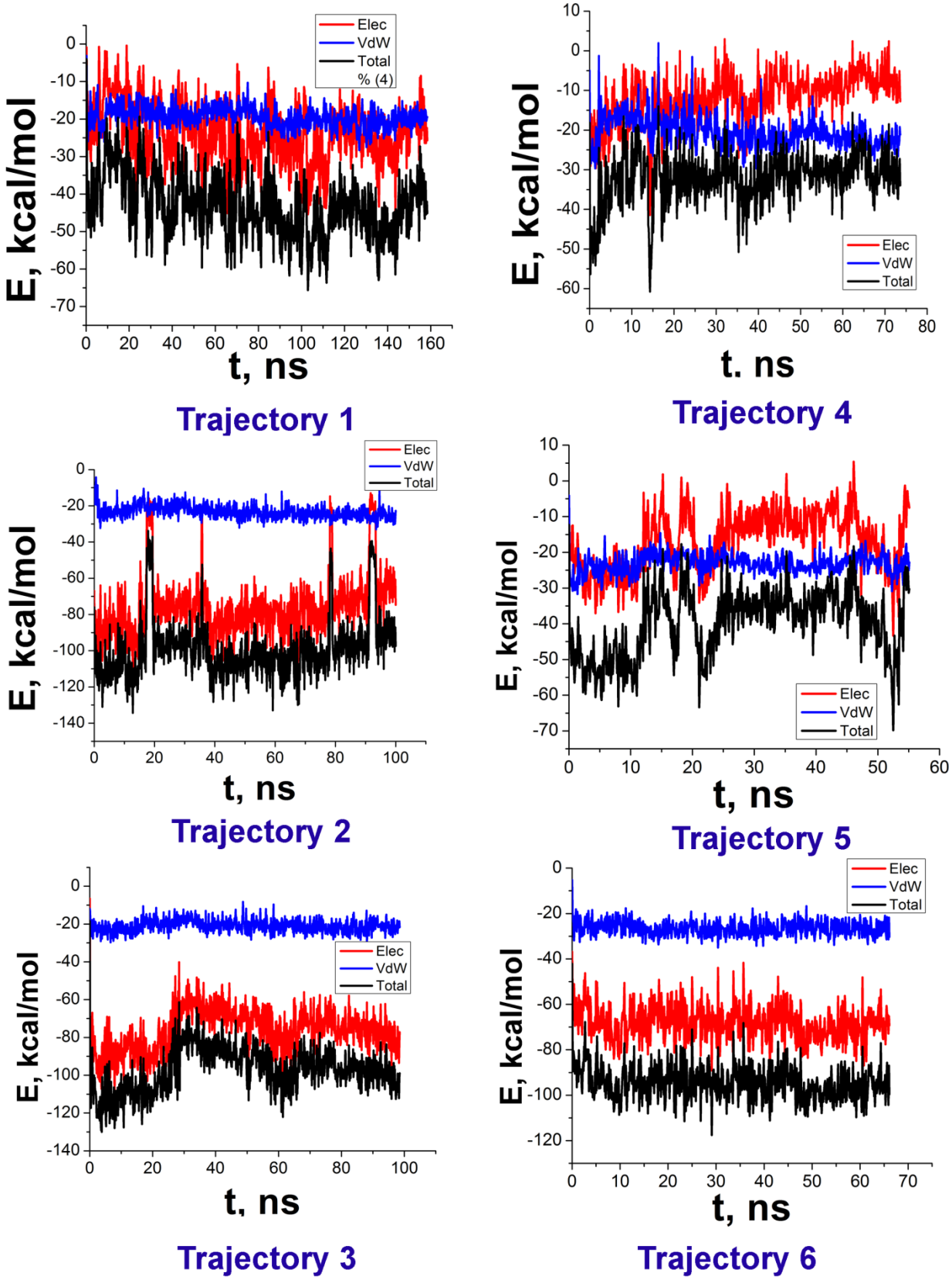


Figure S5. The variation of the electrostatic, van der Waals and total energy of interaction for the trajectories 1-6.

Table 6. The electrostatic, the van der Waals and the total contributions of the individual amino acid residues to the overall energy of the binding for the trajectories 1-3. The first 10 ns of the trajectories were omitted from calculations. The contributions over -1 kcal/mol are considered as significant and represented in bold.

Residue	Trajectory 1			Trajectory 2			Trajectory 3		
	Elec.	VdW	Total	Elec.	VdW	Total	Elec	VdW	Total
Tyr72	-0.390	-0.261	-0.651	0.045	/	0.044	0.017	/	0.017
Asp74	-0.465	-0.226	-0.691	-56.800	2.167	**-54.633**	-7.059	-0.875	**-7.934**
Thr75	-0.811	-0.391	**-1.202**	-1.026	-0.283	**-1.309**	0.222	-0.703	-0.481
Leu76	-1.565	-1.272	**-2.837**	0.040	-0.038	0.002	-0.137	-0.710	-0.846
Tyr77	0.288	-1.689	**-1.401**	0.047	-0.263	-0.216	/	/	/
Thr83	-0.153	-0.498	-0.651	0.061	-0.356	-0.294	/	/	/
Met85	/	/	/	-4.318	-1.087	**-5.405**	-0.197	/	-0.206
Trp86	-1.459	-2.785	**-4.244**	-1.980	-3.588	**-5.569**	-4.826	-1.134	**-5.961**
Trp117	/	/	/	0.240	-0.188	0.052	0.041	/	0.039
Tyr119	0.016	/	0.013	-0.506	-0.443	-0.949	0.582	-0.479	0.103
Gly121	0.518	-0.401	0.117	-0.641	-1.281	**-1.923**	-0.281	-1.001	**-1.282**
Tyr124	-2.962	-0.743	**-3.705**	0.349	-1.203	-0.853	0.267	-2.417	**-2.150**
Gly126	0.048	-0.055	/	/	-0.033	-0.033	0.582	-0.479	0.103
Leu130	0.021	-0.028	/	-0.954	-1.270	**-2.224**	0.201	-0.750	-0.549
Val132	/	-0.011	/	0.050	-0.271	-0.221	-0.013	/	-0.012
Trp286	/	-0.160	-0.154	/	/	/	-0.035	-0.183	-0.218
Leu289	/	/	/	/	/	/	-0.022	/	-0.019
Glu292	0.015	-0.012	/	/	-0.273	-0.268	-0.034	-0.014	-0.049
Val294	-2.133	-0.100	**-2.233**	-5.611	-1.581	**-7.192**	-1.997	-1.391	**-3.387**
Phe295	0.561	-0.246	0.316	-0.571	-1.956	**-2.527**	-0.119	-0.883	**-1.001**
Arg296	-3.321	-0.929	**-4.251**	1.895	-0.969	0.926	-0.568	-0.172	-0.741
Tyr337	-0.445	-0.613	**-1.058**	0.014	/	0.013	/	/	-0.010
Phe338	-0.311	-0.900	**-1.212**	-2.176	-2.493	**-4.668**	-2.176	-2.493	**-4.668**
Leu339	/	/	/	/	/	/	-0.373	-1.273	**-1.646**
Tyr341	-7.206	-1.806	**-9.012**	-1.433	-0.103	**-1.536**	0.151	-0.217	-0.066
Ala343	-0.448	-0.442	-0.891	-1.352	-1.046	**-2.398**	-0.383	-0.762	**-1.145**
Val365	/	/	/	-0.212	-0.726	-0.939	0.034	-0.035	/
Ile451	/	/	/	0.298	-0.217	0.080	/	/	-0.010

Table 7. The electrostatic, the van der Waals and the total contributions of the individual amino acid residues to the overall energy of the binding for the trajectories 4-6. The first 10 ns of the trajectories were omitted from calculations. The contributions over -1 kcal/mol are considered as significant and represented in bold.

Residue	Trajectory 4			Trajectory 5			Trajectory 6		
	Elec	**VdW**	**Total**	**Elec**	**VdW**	**Total**	**Elec**	**VdW**	**Total**
Tyr72	-0.327	-1.614	**-1.941**	-0.708	-0.712	**-1.420**	-1.506	-0.967	**-2.473**
Asp74	-0.563	-0.182	-0.745	-2.435	-0.212	**-2.646**	-0.132	/	-0.141
Thr75	-2.208	-1.083	**-3.291**	-0.071	-0.054	-0.125	0.078	/	0.075
Leu76	-0.083	-1.887	**-1.970**	-0.039	-0.160	-0.199	0.093	-0.628	-0.535
Tyr77	-0.180	-0.417	-0.597	/	/	/	/	/	/
Thr83	0.128	-0.426	-0.298	/	/	/	-0.011	/	-0.013
Met85	/	/	/	-0.047	-0.015	-0.062	/	/	/
Trp86	-0.636	-1.741	**-2.378**	-1.072	-2.944	**-4.016**	-2.489	-5.550	**-8.038**
Trp117	/	/	/	/	/	/	0.061	/	0.059
Tyr119	-0.020	/	-0.017	0.059	-0.014	0.045	0.950	-0.338	0.611
Gly121	0.689	-0.538	0.151	0.215	-1.096	-0.881	3.624	-2.463	**1.161**
Tyr124	-4.161	-1.309	**-5.470**	-1.915	-3.776	**-5.692**	-0.982	-4.118	**-5.100**
Gly126	/	/	/	0.289	-0.271	0.017	0.992	-0.166	0.826
Leu130	/	/	/	0.133	-0.159	-0.026	0.106	-0.271	-0.166
Val132	/	/	/	/	/	/	/	/	/
Trp286	-0.404	-3.682	**-4.086**	-1.200	-1.936	**-3.136**	-0.720	-3.445	**-4.165**
Leu289	/	/	/	0.357	-0.774	-0.417	0.176	-0.115	0.061
Glu292	-0.292	-0.046	-0.337	-2.458	-0.450	**-2.908**	-0.012	/	-0.013
Val294	0.269	-0.326	-0.058	-1.083	-0.683	**-1.766**	-1.126	-0.127	**-1.253**
Phe295	0.309	-0.026	0.283	-0.224	-0.656	-0.880	0.035	/	0.032
Arg296	-0.012	/	-0.010	-2.021	-0.305	**-2.326**	-1.905	-0.197	**-2.102**
Tyr337	-0.891	-0.900	**-1.791**	-0.244	-0.715	-0.959	-1.639	-2.142	**-3.781**
Phe338	-0.341	-1.275	**-1.616**	0.329	-1.059	-0.730	0.529	-0.643	-0.114
Leu339	/	/	/	/	/	/	/	/	/
Tyr341	-0.426	-2.393	**-2.819**	0.036	-1.478	**-1.442**	-0.625	-1.919	**-2.545**
Ala343	-0.020	-0.007	-0.027	0.054	-0.160	-0.106	-0.012	-0.002	-0.013
Val365	0.011	-0.012	-0.001	0.056	/	0.055	/	/	/
Ile451	/	/	/	0.021	-0.008	0.012	/	/	/