Electronic Supplementary Material (ESI) for Physical Chemistry Chemical Physics.

How oxidized EGCG remodels α-synuclein fibrils into non-toxic aggregates: insights from computational simulations

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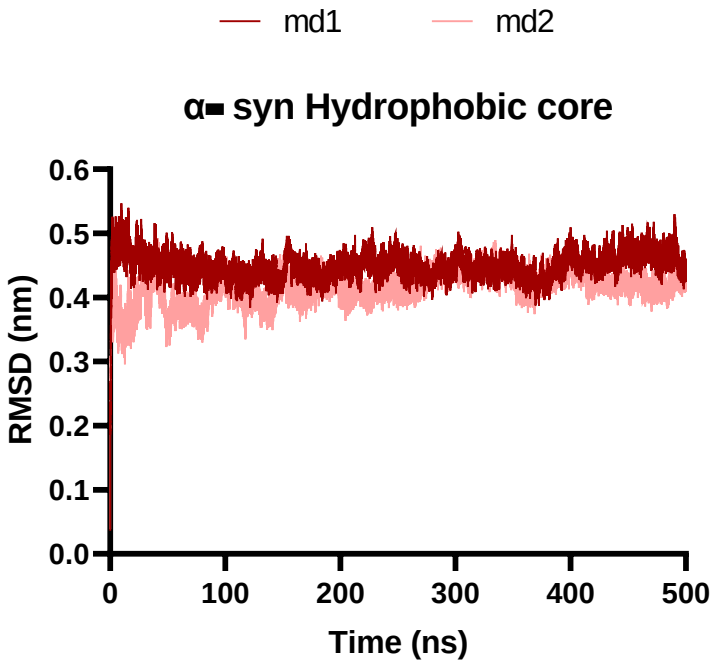
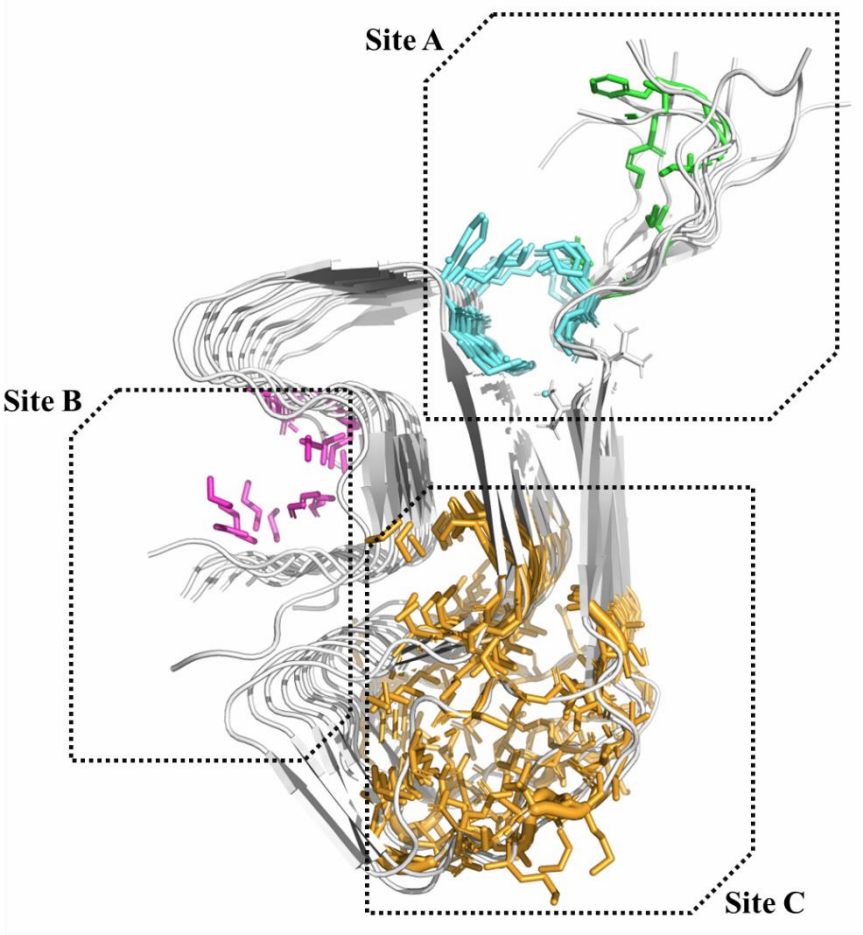


Figure S1. Backbone RMSD values of α-syn hydrophobic core in the two independent replicas as a function of simulation time



Main Residues		
Site A	**Site B**	**Site C**
TYR39, VAL40, SER42, THR44, LYS45, GLU46, GLY47, ALLA78, GLN79, LYS80	GLY86, SER87. ILE88, PHE94, LYS96	ALA53, THR54, VAL55, ALA56, GLU57, LYS58, THR59, LYS60, GLU61, GLN62, VAL63, THR64, ASN65, VAL66, VAL70, VAL71, THR72, GLY73, VAL74, THR75, THR92

Figure S2. Lys-rich sites found within the hydrophobic core of α-syn fibril. Main residues from each site shown in sticks colored in green and cyan (Site A), magenta (Site B), and orange (Site C).

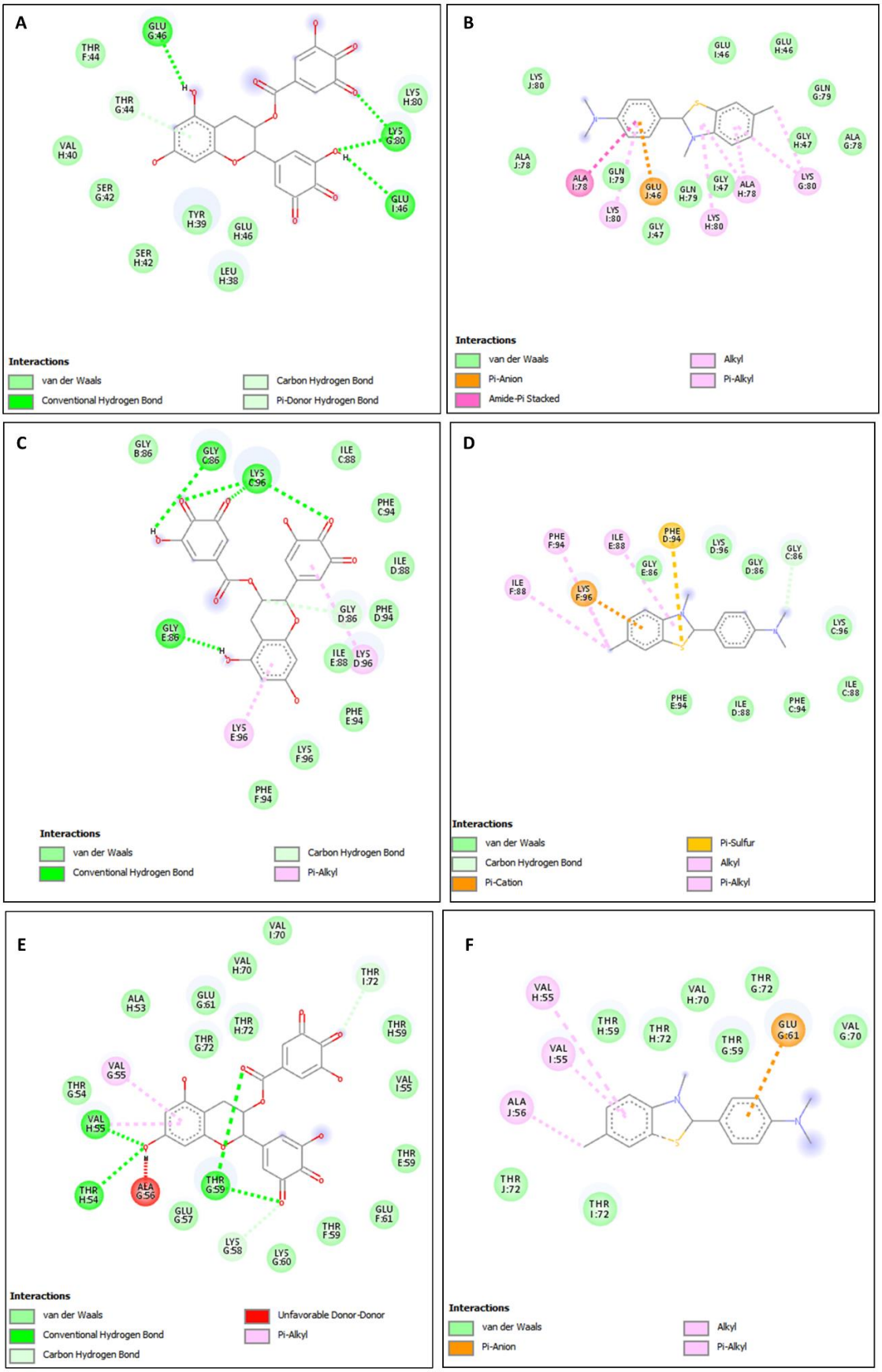


Figure S3. 2D ligand interaction diagrams of oxidized EGCG, (left) and ThT (right) bound in site A (A, B), in site B (C, D), and site C (D, E).

Table S1. Average values of backbone RMSD, SASA, and RG from MD trajectories for two replicas of each system.

Parameters	***Altered α-syn***		***Sites***	***with EGCG***		***with ThT***	
	md1	md2		md1	md2	md1	md2
RMSD (nm)	0.26	0.28	A	0.33	0.28	0.22	0.22
			B	0.20	0.23	0.25	0.22
			C	0.21	0.22	0.27	0.25
SASA (nm\S2\N)	242.22	244.74	A	248.18	247.08	244.27	249.16
			B	247.09	248.14	244.93	240.87
			C	242.69	242.15	240.43	246.53
RG (nm)	2.45	2.43	A	2.43	2.44	2.44	2.45
			B	2.45	2.45	2.44	2.44
			C	2.45	2.45	2.44	2.45

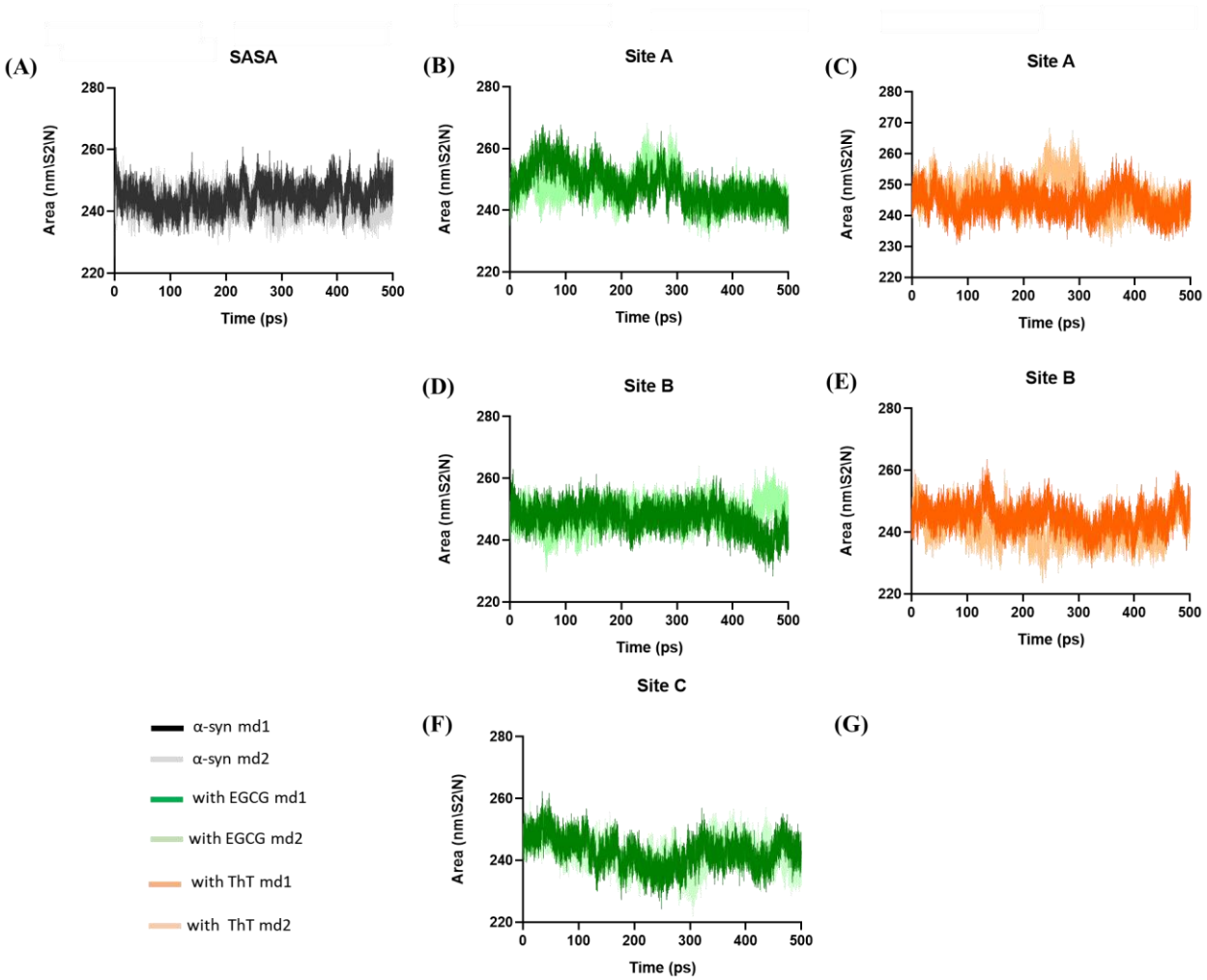


Figure S4. SASA values of α-syn hydrophobic core in the absence of any ligand (black and light gray) and presence of oxidized EGCG (dark and light green) or ThT (dark and light orange) in two independent MD simulations.

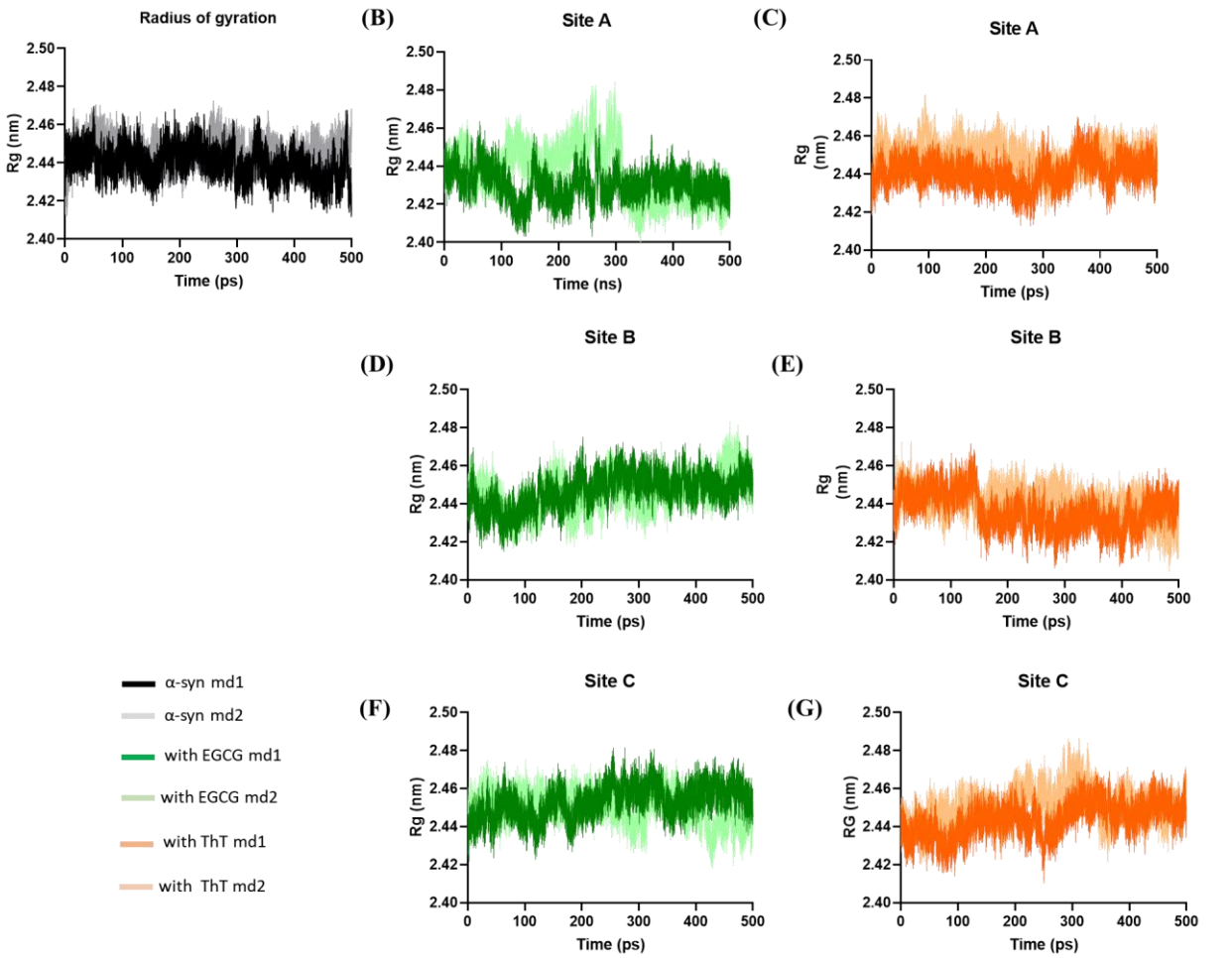


Figure S5. Rg values of α-syn hydrophobic core in the absence of any ligand (black and light gray) and presence of oxidized EGCG (dark and light green) or ThT (dark and light orange) in two independent MD simulations.

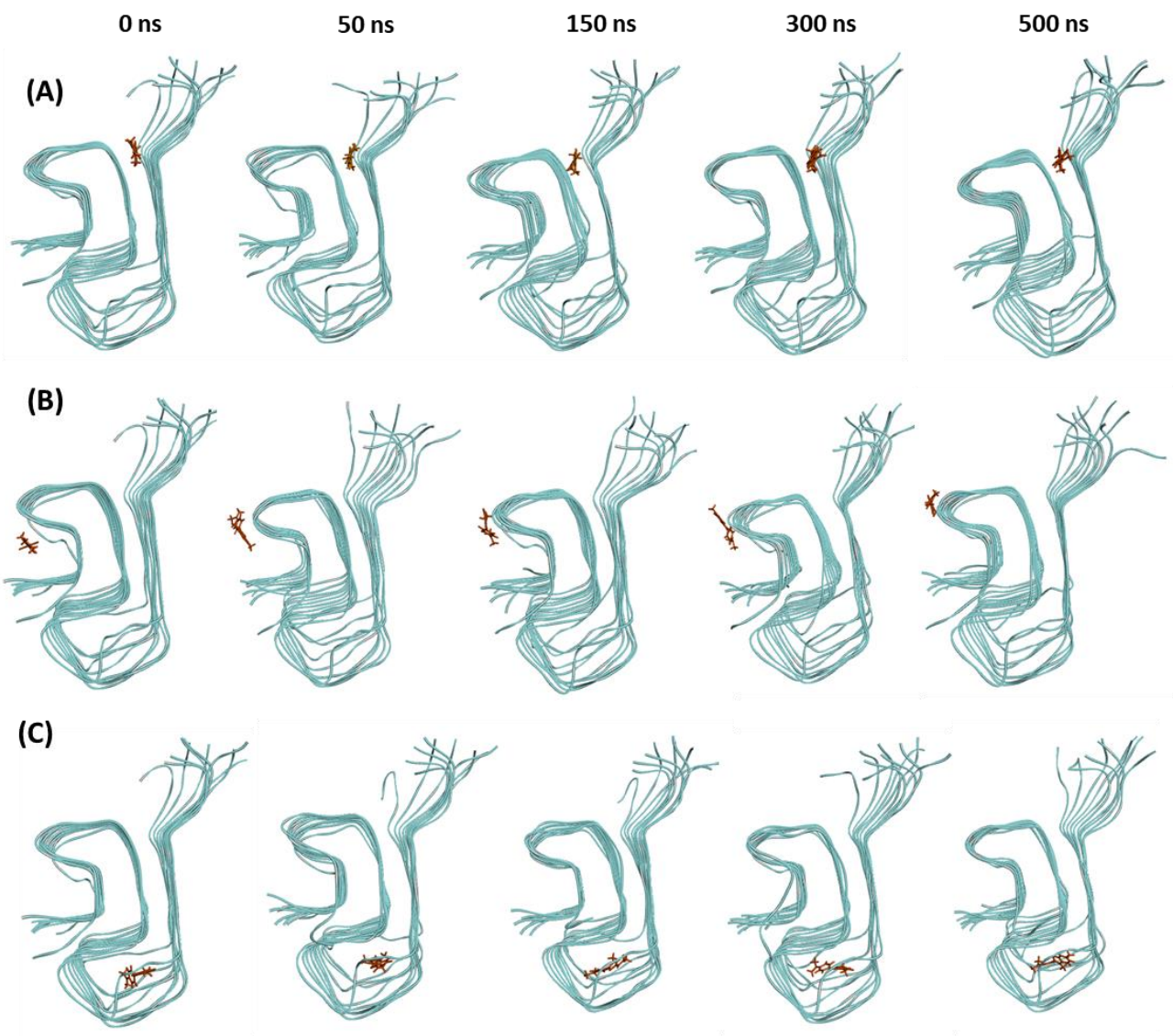


Figure S6. Representative snapshots of α-syn hydrophobic core in the presence of ThT docked in sites A (A), B (B), and C (C) at 0, 50, 150, 300, and 500 ns for run 1. α-syn structure in cyan and ThT (as orange sticks).

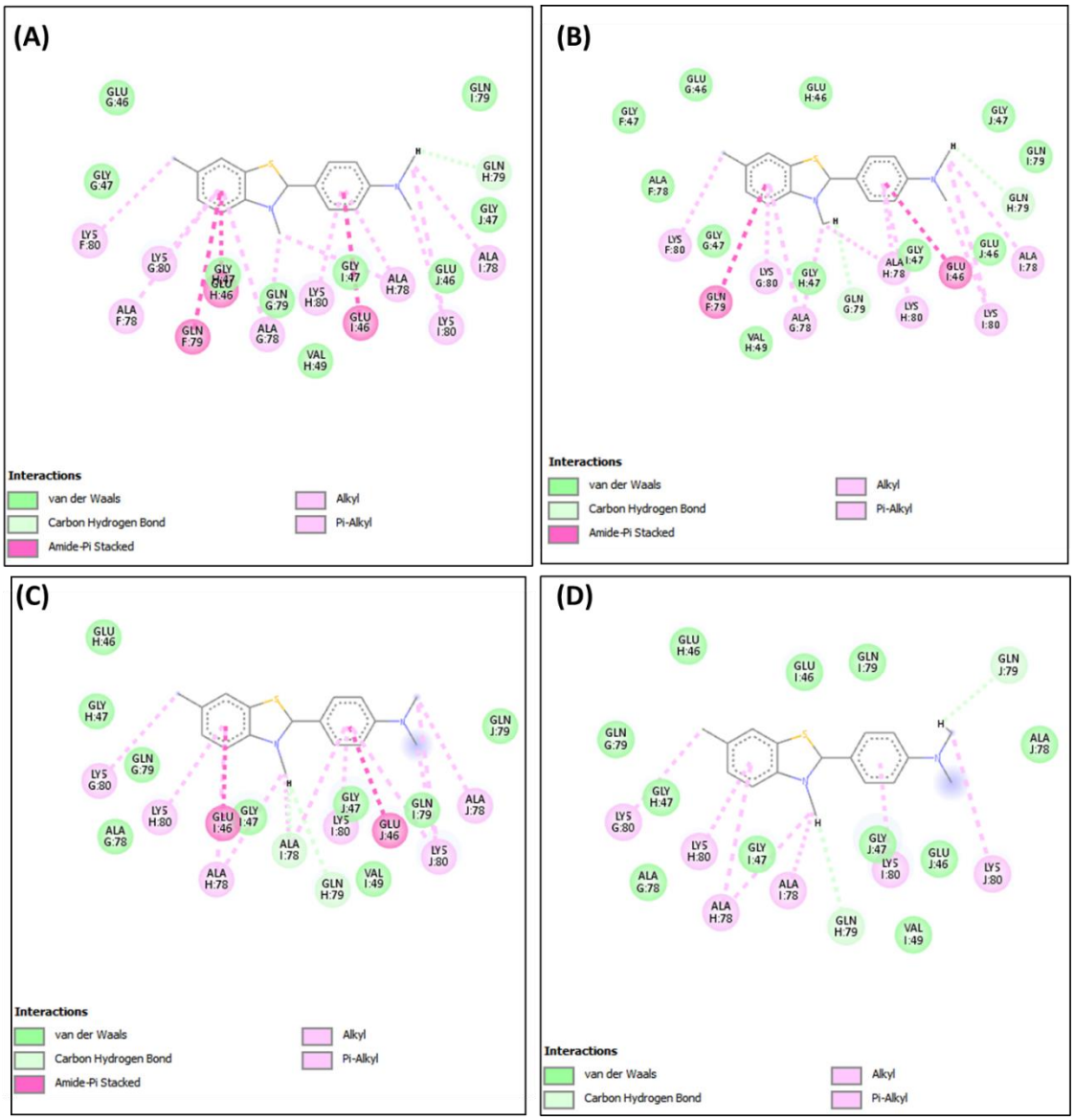


Figure S7. 2D ligand interaction diagrams for ThT docked in site A at 50 ns (A), 150 ns (B), 300 ns (C), and 500 ns (D) for run 1.

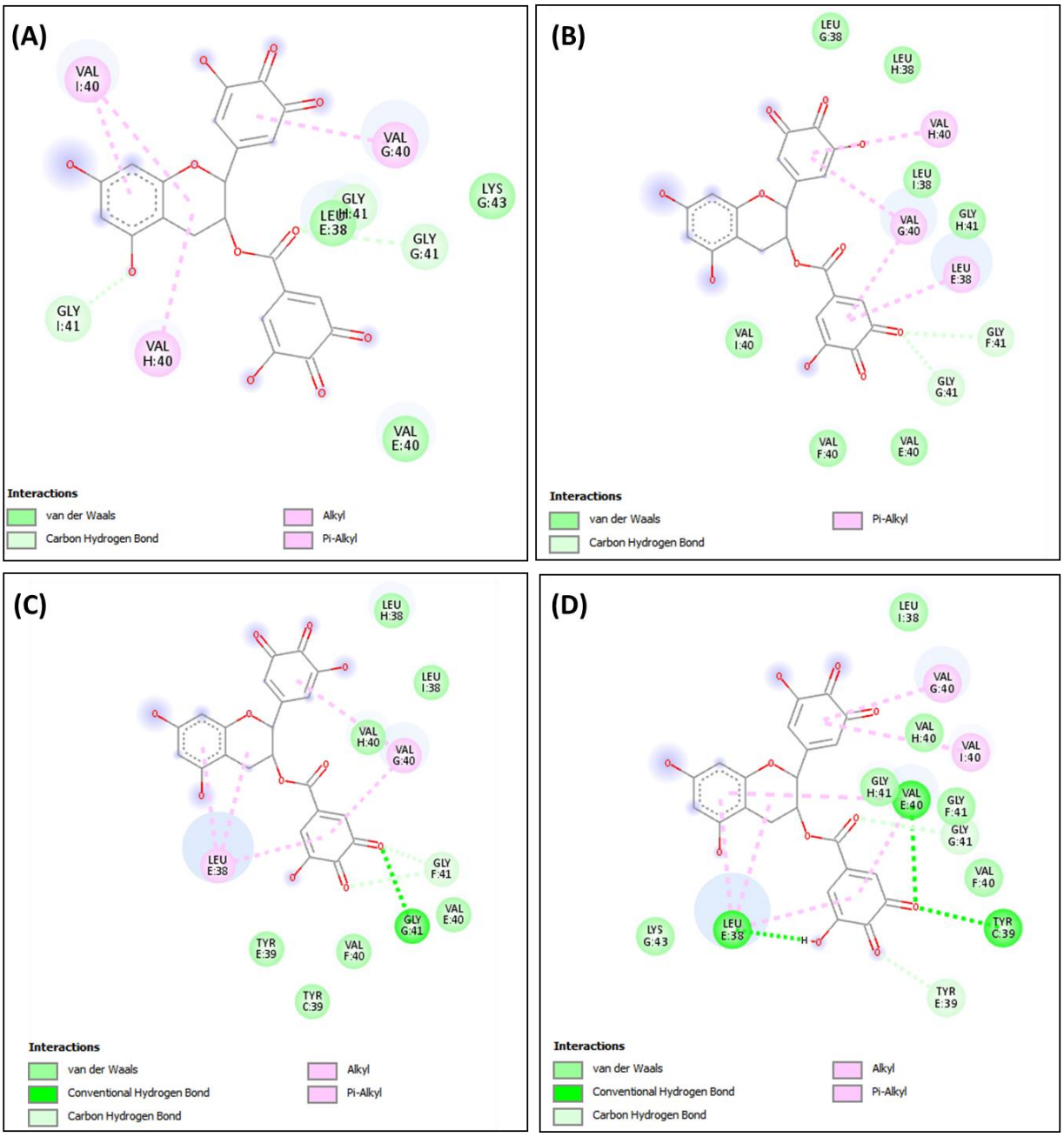


Figure S8. 2D ligand interaction diagrams for oxidized EGCG docked in site A at 50 ns (A), 150 ns (B), 300 ns (C), and 500 ns (D) for run 1.

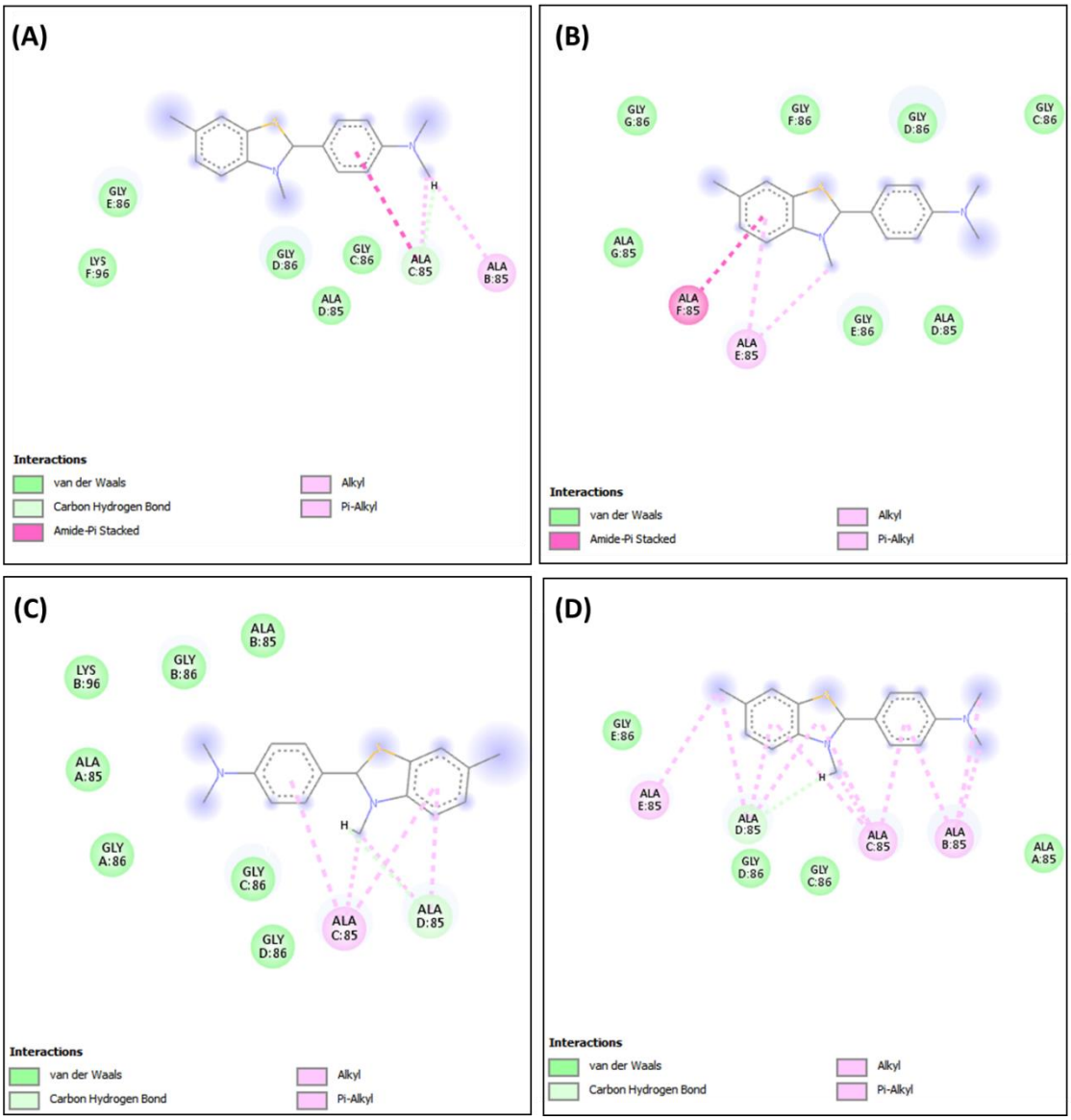


Figure S9. 2D ligand interaction diagrams for ThT docked in site B at 50 ns (A), 150 ns (B), 300 ns (C), and 500 ns (D) for run 1.

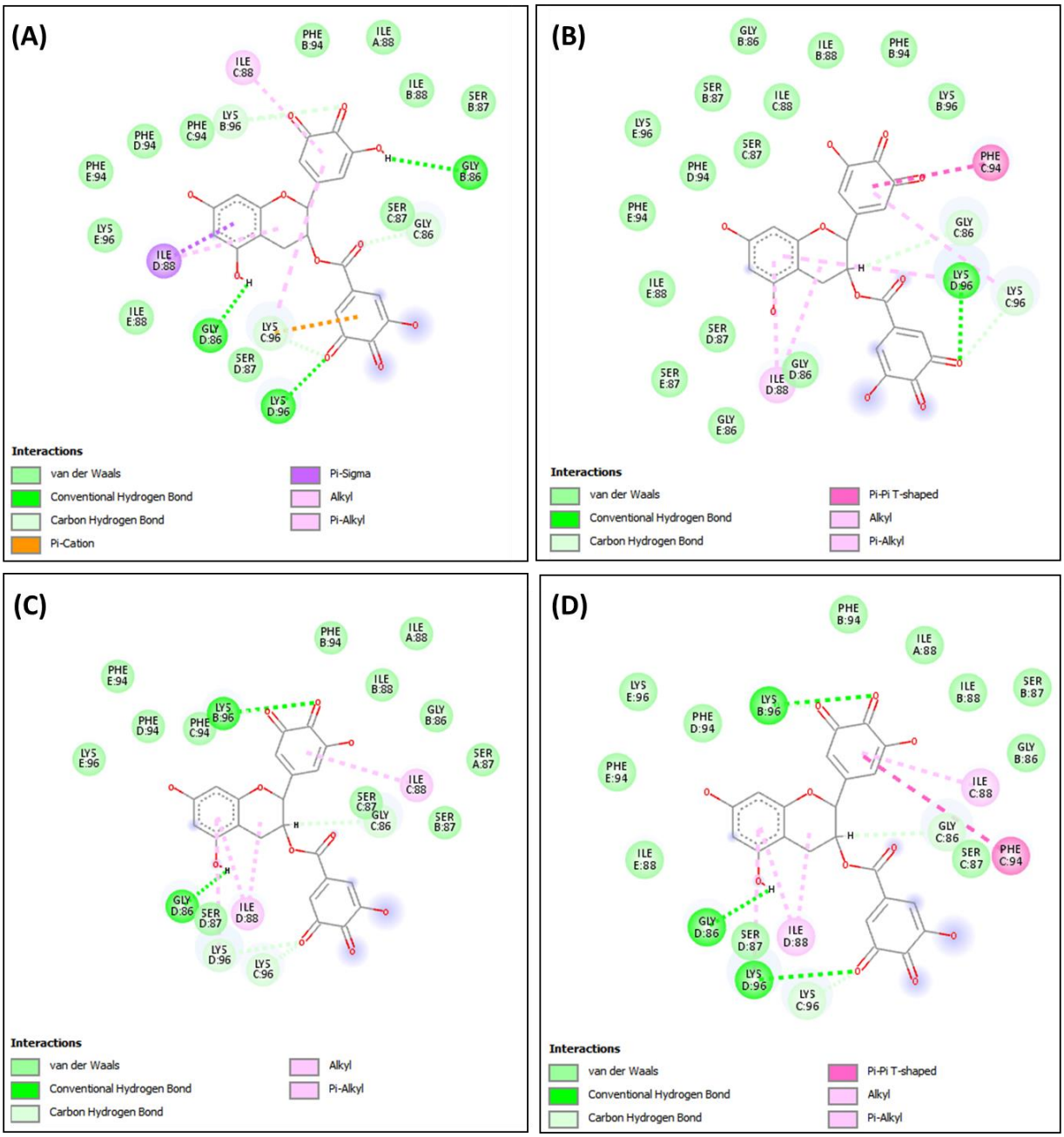


Figure S10. 2D ligand interaction diagrams for oxidized EGCG docked in site B at 50 ns (A), 150 ns (B), 300 ns (C), and 500 ns (D) for run 1.

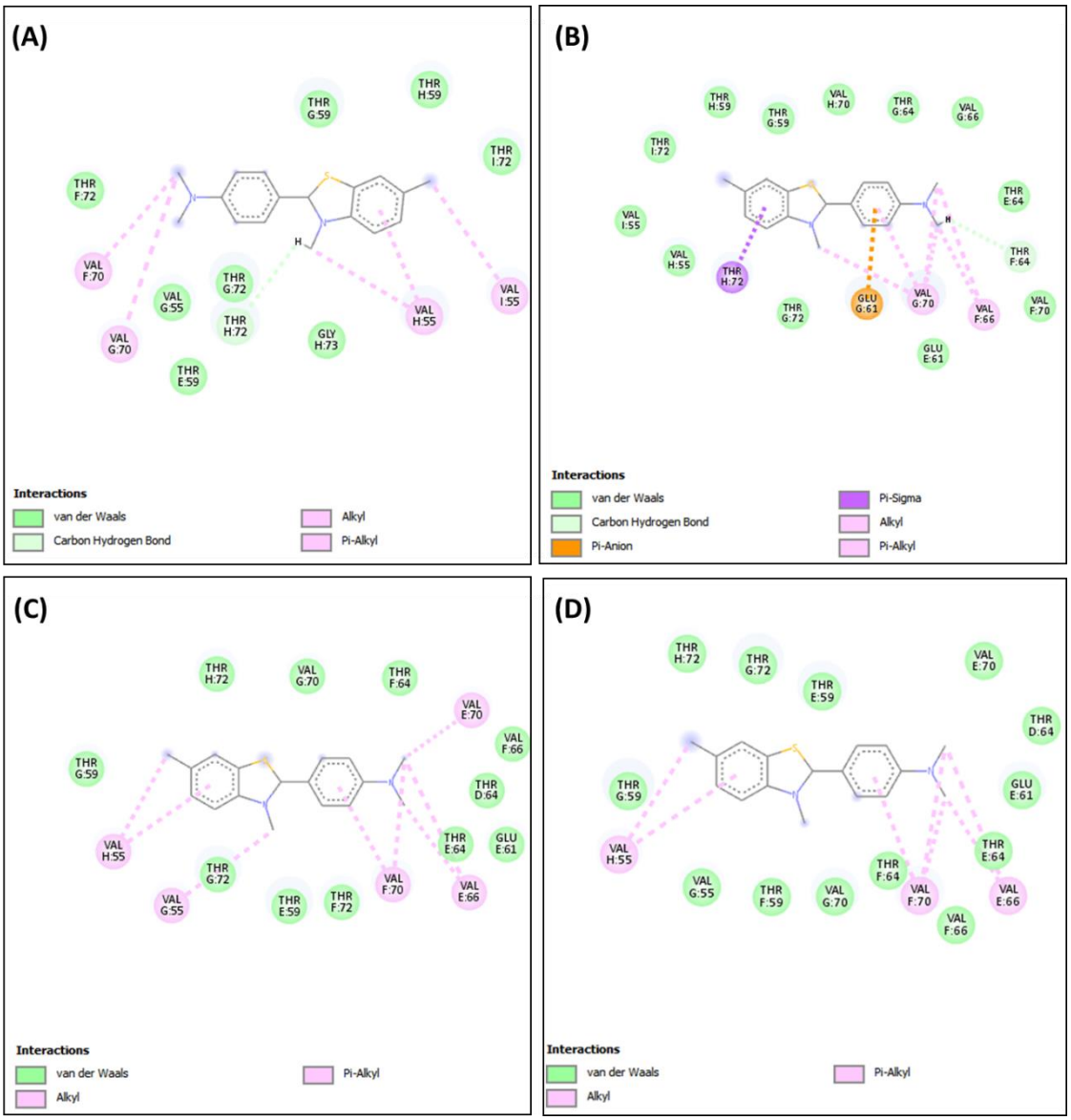


Figure S11. 2D ligand interaction diagrams for ThT docked in site C at 50 ns (A), 150 ns (B), 300 ns (C), and 500 ns (D) for run 1.

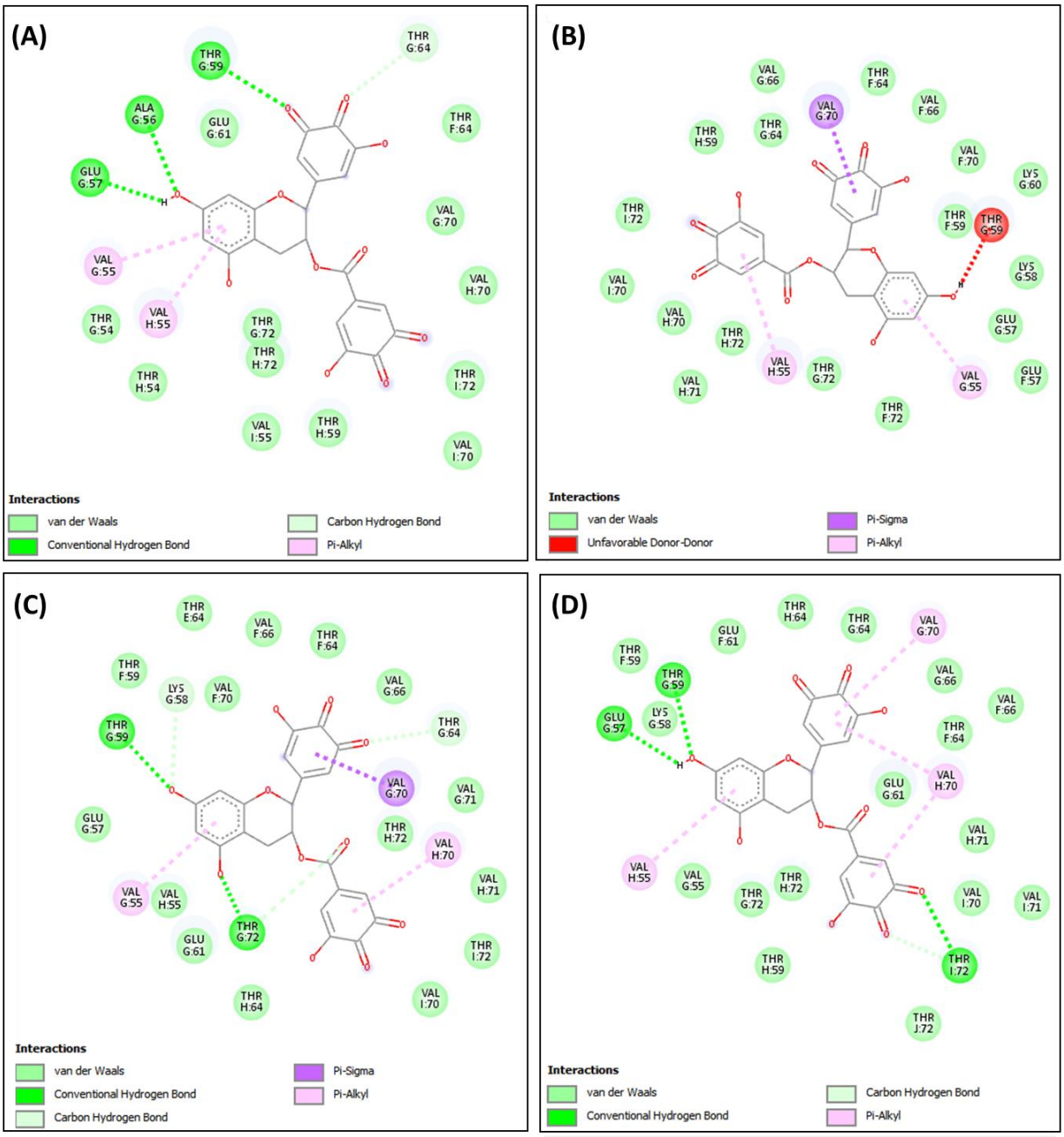


Figure S12. 2D ligand interaction diagrams for oxidized EGCG docked in site C at 50 ns (A), 150 ns (B), 300 ns (C), and 500 ns (D) for run 1.

Table S2. Distances between EGCG and specific residues over 500 ns simulation.

Site	Residues	Chains	Groups	Distance (Å)*		Distance within 3.5 Å**	
				Md1	Md2	Md1	Md2
A	LEU38	E	=O	3.52	7.21	65.83%	2.89%
	TYR39	C	-OH	3.41	10.59	74.32%	0%
	VAL40	G	Alkyl	2.89	8.77	93.22%	1.22%
	GLY41	G	=O	4.72	8.19	8.65%	0%
	GLU46	G	COO^-	16.4	7.37	0.03%	0.65%
	LYS80	G	$- NH^+_3$	19.5	6.31	0.04%	2%
B	GLY86	B	=O	3.18	5.94	86.04%	0.22%
		C	=O	2.45	3.1	99.87%	86.34%
		D	=O	1.91	2.48	99.94%	99.99%
	SER87	B	=O	3.97	5.84	17.66%	0.05%
		C	=O	3.84	4.03	29.15%	17.49%
		D	=O	4.73	3.86	0.31%	25.93%
	ILE88	B	Alkyl	4.11	8.90	49.20%	0.03%
		C	Alkyl	2.82	2.83	97.98%	95.63%
		D	Alkyl	2.88	2.77	97.48%	98.24%
	PHE94	B	Aromatic ring	2.83	5.04	97.46%	0.76%
		C	Aromatic ring	2.5	2.82	99.95%	97.62%
		D	Aromatic ring	2.46	2.62	99.99%	99.62%
	LYS96	B	$- NH^+_3$	3.4	8.46	59.32%	3.71%
		C	$- NH^+_3$	3.8	3.45	33.79%	60.76%
		D	$- NH^+_3$	3.7	3.82	49.89%	40.84%
C	VAL55	G	alkyl	2.64	2.91	99.68%	93.71%
		H	alkyl	3.18	4.42	73.72%	23.16%
	GLU57	G	=O	2.86	3.72	95.20%	41.60%
	LYS58	G	$- NH^+_3$	6.43	6.29	0.18%	0%
	THR59	G	-OH	3.33	3.95	67.72%	26.92%
	GLU61	G	=O	7.5	7.06	0.73%	0.5%
	THR64	G	-OH	6.06	4.72	15.48%	3.08%
	VAL70	G	alkyl	3.24	2.91	70.93%	93.71%
		H	alkyl	5.82	2.87	12.04%	94.08%
	THR72	G	-OH	3.04	3.89	90.98%	15.86%

*The average distance over 500 ns. ** % Frames with distance between EGCG and specific residues within 0.35 Å.

Table S3. Distances between ThT and specific residues over 500 ns simulation.

Site	Residues	Chains	Groups	Distance (Å)*		Distance within 0.35 Å**	
				Md1	Md2	Md1	Md2
A	GLU46	G	COO^-	6.52	5.15	17.8%	46.88%
	GLU46	H	COO^-	4.05	3.6	48.60%	68.96%
	GLU46	I	COO^-	3.28	3.41	63.45%	62.12%
	GLU46	J	COO^-	3.80	3.87	36.00%	36.94%
	GLY47	H	CH_2	3.5	2.99	54.23%	82.36%
	GLY47	I	CH_2	2.49	2.48	83.39%	62.83%
	GLY47	J	CH_2	2.52	2.45	78.89%	99.97%
	GLN79	G	C=O	3.16	3.01	68.57%	88.44%
	GLN79	H	C=O	2.80	2.75	83.50%	99.69%
	GLN79	I	C=O	2.98	2.95	78.61%	94.76%
	GLN79	J	C=O	5.3	5.02	19.38%	46.39%
	LYS80	G	$- NH^+_3$	4.79	4.23	14.34%	28.42%
	LYS80	H	$- NH^+_3$	4.12	4.04	21.00%	22.56%
	LYS80	I	$- NH^+_3$	4.44	4.29	12.04%	16.97%
	LYS80	J	$- NH^+_3$	5.22	5.94	18.95%	8.32%
B	ALA85	A	alkyl	28.7	3.78	1.02%	40.70%
	ALA85	B	alkyl	27.9	37.6	1.32%	0.49%
	ALA85	C	alkyl	27.4	37.3	1.99%	0.66%
	ALA85	D	alkyl	27.4	37.1	3.73%	0.87%
	GLY86	A	=O	31.6	38.7	0.11%	0.09%
B		B	=O	30.7	38.4	0.12%	0.17%
		C	=O	38.1	38.1	0.22%	0.22%
		D	=O	29.8	1.33	37.9	0.35%
C	VAL55	G	alkyl	5.50	3.05	17.07%	80.90%
		H	alkyl	6.07	5.83	20.67%	6.03%
	THR59	E	-OH	3.02	4.84	84.66%	2.63%
		G	-OH	4.85	6.07	5.38%	9.54%
	THR64	E	-OH	4.76	6.75	2.67%	0.29%
		G	-OH	4.03	6.47	46.66%	32.71%
	VAL66	E	alkyl	2.90	6.20	86.61%	2.90%
		F	alkyl	3.24	5.49	73.82%	25.07%
		G	alkyl	4.55	6.29	18.59%	32.20%
	VAL70	E	alkyl	3.35	4.19	68.12%	45.47%
		F	alkyl	2.86	3.19	95.12%	68.91%
	THR72	F	-OH	4.52	3.34	17.15%	66.32%
		G	-OH	4.69	4.57	30.42%	12.89%
		H	-OH	4.85	6.60	31.53%	4.97%

*The average distance over 500 ns. ** % Frames with distance between EGCG and specific residues within 0.35 Å

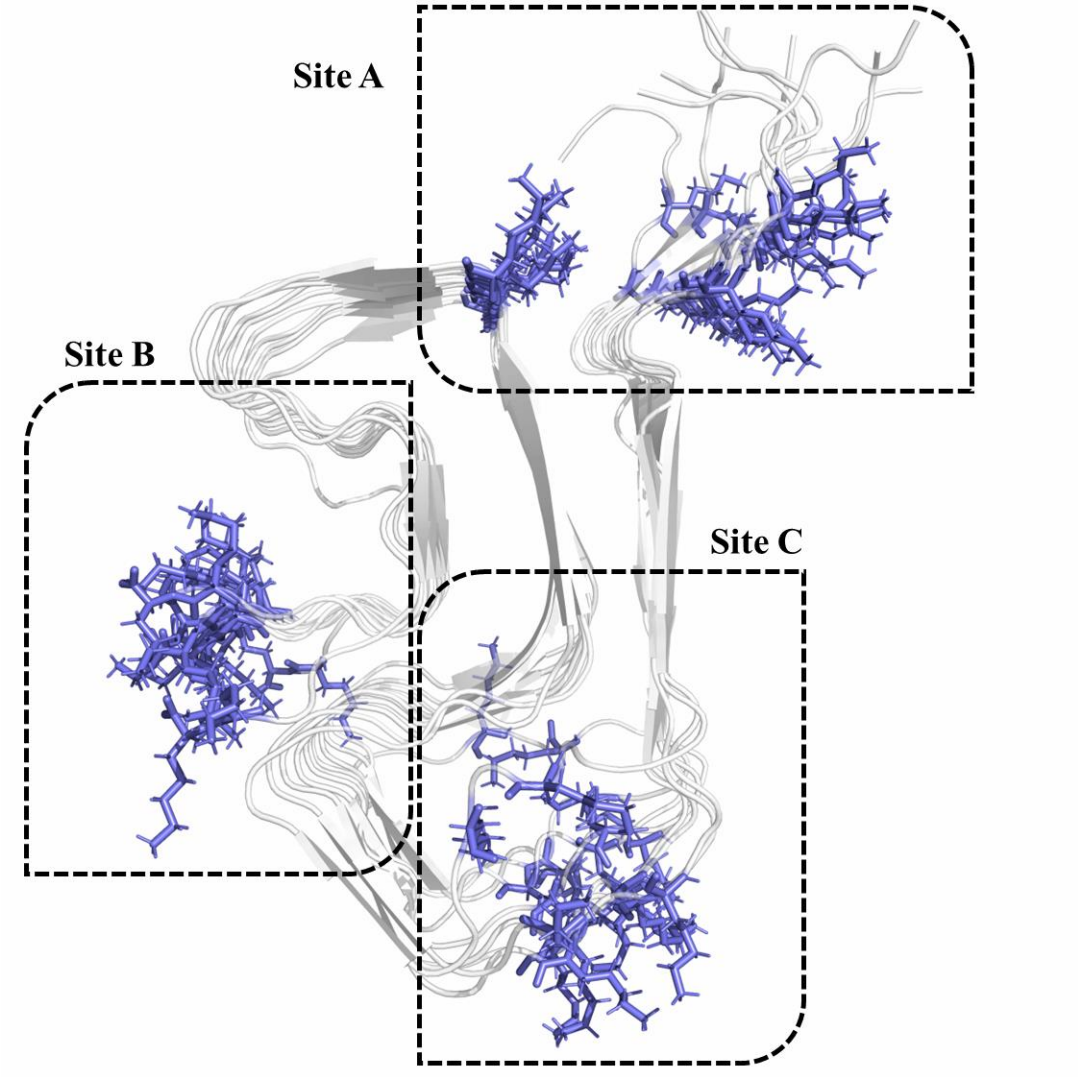


Figure S13. Three Lys-rich sites were selected for docking search, named as site A, B, and C. The Lys residues are shown in blue sticks.