Int. J. Nano Dimens., 11 (4): 312-336, Autumn 2020

ORIGINAL ARTICLE

Tripeptide arginyl-glycyl-aspartic acid (RGD) for delivery of Cyclophosphamide anticancer drug: A computational approach

Zahra Nikfar, Zahra Shariatinia*

Department of Chemistry, Amirkabir University of Technology (Tehran Polytechnic), Tehran, Iran.

Received 09 July 2020; revised 11 August 2020; accepted 15 August 2020; available online 17 August 2020

Abstract

Density functional theory (DFT) calculations were performed on tripeptide arginyl-glycyl-aspartic acid (RGD) as an efficient drug carrier to deliver the commercially famous cyclophosphamide (CP) anticancer drug within ethanol solution. The most negative binding energy (-5.22 kcal/mol) was measured for the CP-RGD-7 created through the H-bond interaction between the P=O (phosphoryl) oxygen atom of the CP and hydrogen atom of O-H group in the RGD. The quantum theory of atoms in molecules (QTAIM) proved that the CP-RGD-6 was composed of five intra-molecular CH…HC, N…HC and NH…OC plus one inter-molecular NH…N interactions. Among CP-RGD-6, CP-RGD-7 and CP-RGD-8 with the smallest binding energies (highest structural stabilities), the CP-RGD-6 showed the minimum hardness, energy gap and chemical potential whereas the utmost electrophilicity index and electronegativity which confirmed it could the most effectively be bound onto the cancer cells. Consequently, among twenty designed carriers, the CP-RGD-6 was recognized as the most promising drug delivery system. According to the results achieved from the molecular dynamics (MD) simulations performed in ethanol solvent on the CP-RGD-PEG systems containing different number of PEG chains, it was established that the CP-RGD-6PEG cell was the most suitable vehicle with desirable FV (4988.89 Å^3) and FFV (22.66%) values as well as small drug diffusion coefficient (0.0114×10^{-5} cm^2/s) indicating low drug release rate.

Keywords: *Cyclophosphamide Anticancer Drug; DFT Computations; Drug Delivery; MD Simulations; Tripeptide RGD.*

How to cite this article

Nikfar Z., ShariatiniaZ. Tripeptide arginyl-glycyl-aspartic acid (RGD) for delivery of Cyclophosphamide anticancer drug: A computational approach. Int. J. Nano Dimens., 2020; 11 (4): 312-336.

* Corresponding Author Email: *shariati@aut.ac.ir*

Table S1. The bond lengths (Å) and angles (◦) for the CP, RGD, CP-RGD-1, CP-RGD-6, CP-RGD-7, CP-RGD-8 and CP-RGD-10 optimized at B3LYP/6-31+G(d,p) level of theory.

CP				**CP-RGD-1**			
Bond length		Bond angle		Bond length		Bond angle	
P–O1	1.50	C1–C2–C3	112.02	P–O1	1.51	C1–C2–C3	111.55
P–O2	1.62	C1–N1–P	118.10	P–O2	1.62	C1–N1–P	120.12
P–N1	1.67	N1–P–O1	113.55	P–N1	1.67	N1–P–O1	117.56
P–N2	1.69	N1–P–O2	107.09	P–N2	1.67	N1–P–O2	102.08
N1–H1	1.01	N1–P-N2	103.62	N1–H1	1.02	N1–P-N2	107.46
N1–C1	1.48	P–N2–C4	120.39	N1–C1	1.48	P–N2–C4	120.27
N2–C4	1.47	P–N2–C5	120.04	N2–C4	1.47	P–N2–C5	120.92
N2–C5	1.47	C4–N2–C5	117.95	N2–C5	1.47	C4–N2–C5	118.80
		RGD		O1…H9	1.83	P–O1…H9	129.99
N3–C6	1.39	N3–C6–N4	119.49	N3–C6	1.39	N3–C6–N4	119.48
N4–C6	1.30	N3–C6–N5	113.47	N4–C6	1.30	N3–C6–N5	113.43
N5–C6	1.38	N4–C6–N5	127.03	N5–C6	1.38	N4–C6–N5	127.08
N5–C7	1.46	C6–N5–C7	121.88	N5–C7	1.46	C6–N5–C7	121.90
N6–C10	1.47	C9–C10–N6	115.13	N6–C10	1.47	C9–C10–N6	110.91
N7–C11	1.34	N6–C10–C11	111.18	N7–C11	1.35	N6–C10–C11	109.15
N7–C12	1.44	C10–C11–N7	115.46	N7–C12	1.45	C10–C11–N7	114.99
N8–C13	1.35	N7–C11–O3	123.03	N8–C13	1.35	N7–C11–O3	122.26
N8–C14	1.45	C11–N7–C12	122.95	N8–C14	1.46	C11–N7–C12	122.88
C11–O3	1.24	N7–C12–C13	109.44	C11–O3	1.24	N7–C12–C13	108.91
C13–O4	1.24	O4–C13–N8	122.84	C13–O4	1.24	O4–C13–N8	124.25
C15–O5	1.34	N8–C14–C15	107.71	C15–O5	1.34	N8–C14–C15	108.13
C15–O6	1.22	N8–C14–C16	112.19	C15–O6	1.22	N8–C14–C16	111.06
C17–O7	1.22	C7–C8–C9	111.93	C17–O7	1.22	C7–C8–C9	111.71
C17–O8	1.35	C15–C14–C16	111.58	C17–O8	1.35	C15–C14–C16	111.63
C7–C8	1.53	C14–C16–C17	113.29	C7–C8	1.53	C14–C16–C17	112.45
C9–C10	1.54	C10–C11–O3	121.49	C9–C10	1.54	C10–C11–O3	122.74
C10–C11	1.54	C12–C13–O4	122.18	C10–C11	1.54	C12–C13–O4	121.27
C12–C13	1.53	O5–C15–O6	123.88	C12–C13	1.53	O5–C15–O6	123.29
C14–C15	1.53	O7–C17–O8	122.94	C14–C15	1.53	O7–C17–O8	123.02
C14–C16	1.55	H10–O5–C15	108.97	C14–C16	1.53	H10–O5–C15	108.91
C16–C17	1.51	H11–O8–C17	108.43	C16–C17	1.51	H11–O8–C17	108.59
N4–H4	1.02	H9–N8–C13	120.40	N4–H4	1.02	H9–N8–C13	119.13
N5–H5	1.01	H9–N8–C14	116.84	N5–H5	1.01	H9–N8–C14	118.72
N7–H8	1.02	H2–N3–H3	112.39	N7–H8	1.01	H2–N3–H3	112.40
N8–H9	1.01	H4–N4–C6	111.22	N8–H9	1.03	H4–N4–C6	111.31
O5–H10	0.97	H5–N5–C6	115.05	O5–H10	0.97	H5–N5–C6	115.06
O8–H11	0.97	H6–N6–H7	107.07	O8–H11	0.97	H6–N6–H7	105.99

Table S1. Continued.

CP-RGD-6	**CP-RGD-7**

Bond length		Bond angle		Bond length		Bond angle	
P–O1	1.50	C1–C2–C3	111.83	P–O1	1.51	C1–C2–C3	111.97
P–O2	1.62	C1–N1–P	118.45	P–O2	1.61	C1–N1–P	119.37
P–N1	1.65	N1–P–O1	113.26	P–N1	1.66	N1–P–O1	112.35
P–N2	1.70	N1–P–O2	108.06	P–N2	1.69	N1–P–O2	108.31
N1–H1	1.04	N1–P-N2	105.61	N1–H1	1.02	N1–P-N2	105.99
N1–C1	1.48	P–N2–C4	116.12	N1–C1	1.48	P–N2–C4	118.69
N2–C4	1.48	P–N2–C5	118.14	N2–C4	1.48	P–N2–C5	116.08
N2–C5	1.47	C4–N2–C5	115.47	N2–C5	1.48	C4–N2–C5	115.72
O1…H2	1.97	P–O1…H2	121.45	O1…H10	1.56	P–O1…H10	130.80
N3–C6	1.38	N3–C6–N4	119.92	N3–C6	1.39	N3–C6–N4	119.45
N4–C6	1.30	N3–C6–N5	114.32	N4–C6	1.30	N3–C6–N5	113.49
N5–C6	1.38	N4–C6–N5	125.75	N5–C6	1.38	N4–C6–N5	127.06
N5–C7	1.46	C6–N5–C7	122.30	N5–C7	1.46	C6–N5–C7	121.85
N6–C10	1.46	C9–C10–N6	110.56	N6–C10	1.47	C9–C10–N6	109.35
N7–C11	1.35	N6–C10–C11	112.33	N7–C11	1.35	N6–C10–C11	108.22
N7–C12	1.45	C10–C11–N7	116.03	N7–C12	1.45	C10–C11–N7	115.30
N8–C13	1.36	N7–C11–O3	122.47	N8–C13	1.35	N7–C11–O3	122.15
N8–C14	1.45	C11–N7–C12	123.05	N8–C14	1.45	C11–N7–C12	122.56
C11–O3	1.24	N7–C12–C13	108.89	C11–O3	1.24	N7–C12–C13	109.13
C13–O4	1.23	O4–C13–N8	123.45	C13–O4	1.23	O4–C13–N8	123.54
C15–O5	1.34	N8–C14–C15	111.48	C15–O5	1.32	N8–C14–C15	112.06
C15–O6	1.22	N8–C14–C16	111.97	C15–O6	1.23	N8–C14–C16	111.39
C17–O7	1.22	C7–C8–C9	111.96	C17–O7	1.22	C7–C8–C9	111.78
C17–O8	1.35	C15–C14–C16	111.36	C17–O8	1.35	C15–C14–C16	111.65
C7–C8	1.53	C14–C16–C17	112.64	C7–C8	1.53	C14–C16–C17	115.60
C9–C10	1.54	C10–C11–O3	121.49	C9–C10	1.54	C10–C11–O3	122.55
C10–C11	1.54	C12–C13–O4	121.63	C10–C11	1.54	C12–C13–O4	121.62
C12–C13	1.53	O5–C15–O6	123.62	C12–C13	1.53	O5–C15–O6	124.95
C14–C15	1.53	O7–C17–O8	122.92	C14–C15	1.53	O7–C17–O8	122.61
C14–C16	1.53	H10–O5–C15	108.61	C14–C16	1.54	H10–O5–C15	111.94
C16–C17	1.51	H11–O8–C17	108.45	C16–C17	1.51	H11–O8–C17	108.38
N4–H4	1.02	H9–N8–C13	118.73	N4–H4	1.02	H9–N8–C13	118.58
N5–H5	1.01	H9–N8–C14	118.57	N5–H5	1.01	H9–N8–C14	118.54
N7–H8	1.01	H2–N3–H3	113.84	N7–H8	1.01	H2–N3–H3	112.38
N8–H9	1.01	H4–N4–C6	111.72	N8–H9	1.01	H4–N4–C6	111.26
O5–H10	0.97	H5–N5–C6	115.22	O5–H10	1.02	H5–N5–C6	115.10
O8–H11	0.97	H6–N6–H7	106.36	O8–H11	0.97	H6–N6–H7	106.24

Table S1. Continued.

CP-RGD-8				CP-RGD-10			
Bond length		Bond angle		Bond length		Bond angle	
P–O1	1.51	C1–C2–C3	112.22	P–O1	1.50	C1–C2–C3	111.88
P–O2	1.62	C1–N1–P	117.78	P–O2	1.62	C1–N1–P	118.38
P–N1	1.65	N1–P–O1	112.81	P–N1	1.66	N1–P–O1	113.95
P–N2	1.68	N1–P–O2	108.13	P–N2	1.69	N1–P–O2	107.90
N1–H1	1.02	N1–P-N2	105.61	N1–H1	1.02	N1–P-N2	105.06
N1–C1	1.48	P–N2–C4	120.35	N1–C1	1.48	P–N2–C4	121.24
N2–C4	1.47	P–N2–C5	120.20	N2–C4	1.47	P–N2–C5	117.90
N2–C5	1.47	C4–N2–C5	118.24	N2–C5	1.47	C4–N2–C5	115.99
O1…H11	1.59	P–O1…H11	127.90	O6…H1	1.98	O6…H1–N1	173.06
N3–C6	1.39	N3–C6–N4	119.46	N3–C6	1.42	N3–C6–N4	124.52
N4–C6	1.30	N3–C6–N5	113.42	N4–C6	1.29	N3–C6–N5	112.82
N5–C6	1.38	N4–C6–N5	127.12	N5–C6	1.36	N4–C6–N5	122.51
N5–C7	1.46	C6–N5–C7	121.93	N5–C7	1.45	C6–N5–C7	123.40
N6–C10	1.47	C9–C10–N6	109.46	N6–C10	1.47	C9–C10–N6	110.60
N7–C11	1.35	N6–C10–C11	108.07	N7–C11	1.37	N6–C10–C11	115.34
N7–C12	1.45	C10–C11–N7	115.33	N7–C12	1.46	C10–C11–N7	124.31
N8–C13	1.36	N7–C11–O3	122.13	N8–C13	1.36	N7–C11–O3	118.56
N8–C14	1.45	C11–N7–C12	122.51	N8–C14	1.46	C11–N7–C12	131.95
C11–O3	1.24	N7–C12–C13	109.15	C11–O3	1.24	N7–C12–C13	115.53
C13–O4	1.23	O4–C13–N8	123.57	C13–O4	1.23	O4–C13–N8	123.54
C15–O5	1.34	N8–C14–C15	111.72	C15–O5	1.32	N8–C14–C15	108.03
C15–O6	1.22	N8–C14–C16	111.56	C15–O6	1.22	N8–C14–C16	111.01
C17–O7	1.23	C7–C8–C9	111.85	C17–O7	1.22	C7–C8–C9	111.94
C17–O8	1.33	C15–C14–C16	111.48	C17–O8	1.35	C15–C14–C16	112.32
C7–C8	1.53	C14–C16–C17	115.15	C7–C8	1.54	C14–C16–C17	112.53
C9–C10	1.54	C10–C11–O3	122.54	C9–C10	1.55	C10–C11–O3	117.12
C10–C11	1.54	C12–C13–O4	121.71	C10–C11	1.54	C12–C13–O4	119.31
C12–C13	1.53	O5–C15–O6	123.54	C12–C13	1.53	O5–C15–O6	124.94
C14–C15	1.53	O7–C17–O8	124.11	C14–C15	1.54	O7–C17–O8	122.85
C14–C16	1.54	H10–O5–C15	108.56	C14–C16	1.53	H10–O5–C15	108.51
C16–C17	1.52	H11–O8–C17	112.16	C16–C17	1.51	H11–O8–C17	108.51
N4–H4	1.02	H9–N8–C13	118.60	N4–H4	1.02	H9–N8–C13	117.84
N5–H5	1.01	H9–N8–C14	118.36	N5–H5	1.01	H9–N8–C14	118.95
N7–H8	1.01	H2–N3–H3	112.37	N7–H8	1.02	H2–N3–H3	110.62
N8–H9	1.01	H4–N4–C6	111.29	N8–H9	1.01	H4–N4–C6	110.44
O5–H10	0.97	H5–N5–C6	114.97	O5–H10	1.02	H5–N5–C6	117.38
O8–H11	1.01	H6–N6–H7	106.22	O8–H11	0.97	H6–N6–H7	106.20

Table S2. The electron density ($\rho(r)$ in ea_0^{-3}), laplacian of electron density ($\nabla^2\rho(r)$ in ea_0^{-5}), kinetic energy density ($G(r)$ in $e^2a_0^{-4}$), potential energy ($V(r)$ in $e^2a_0^{-4}$), total electronic energy density ($H(r)$ in $e^2a_0^{-4}$) and $|V(r)|/G(r)$ calculated by QTAIM method at B3LYP/6-31+G(d,p) level for bond paths in CP, RGD and compounds **1**, **6**, **7**, **8**, **10**.

	$\rho(r)$	$\nabla^2\rho(r)$	$G(r)$	$V(r)$	$H(r)$	$V(r)/G(r)$
CP						
P–O1	0.223	-0.371	0.525	-1.143	-0.618	-2.177
P–O2	0.168	-0.184	0.295	-0.636	-0.341	-2.157
P–N1	0.181	-0.130	0.277	-0.587	-0.310	-2.117
P–N2	0.173	-0.110	0.251	-0.529	-0.278	-2.109
N1–H1	0.337	0.438	0.057	-0.004	0.053	-0.070
N1–C1	0.250	0.164	0.109	-0.177	-0.068	-1.624
N2–C4	0.254	0.170	0.117	-0.192	-0.075	-1.638
N2–C5	0.255	0.172	0.119	-0.196	-0.076	-1.640
C1–C2	0.248	0.143	0.055	-0.075	-0.020	-1.355
C2–C3	0.252	0.150	0.057	-0.076	-0.019	-1.338
O2–C3	0.227	0.105	0.183	-0.339	-0.156	-1.856
C–Cl1	0.166	0.044	0.055	-0.099	-0.044	-1.800
C–Cl2	0.166	0.044	0.055	-0.099	-0.0443	-1.800
Cl1CH … HCCl2	0.007	-0.007	0.005	-0.011	-0.007	-2.329
RGD						
C6–N3	0.313	0.271	0.165	-0.261	-0.097	-1.588
C6–N4	0.384	0.336	0.298	-0.512	-0.214	-1.718
C6–N5	0.316	0.266	0.200	-0.334	-0.134	-1.667
N5–C7	0.262	0.187	0.130	-0.213	-0.083	-1.640
C7–C8	0.248	0.144	0.0556	-0.075	-0.019	-1.352
C9–C10	0.243	0.136	0.055	-0.076	-0.021	-1.383
N6–C10	0.265	0.183	0.109	-0.173	-0.064	-1.581
C11–O3	0.391	0.048	0.624	-1.235	-0.612	-1.981
C11–N7	0.334	0.239	0.306	-0.552	-0.246	-1.805
C12–N7	0.273	0.204	0.133	-0.214	-0.082	-1.615
O4–C13	0.396	0.034	0.647	-1.286	-0.639	-1.987
C13–N8	0.329	0.245	0.282	-0.504	-0.221	-1.783
C14–N8	0.269	0.197	0.132	-0.214	-0.082	-1.625
C14–C15	0.258	0.161	0.056	-0.072	-0.016	-1.289
C14–C16	0.237	0.131	0.053	-0.074	-0.021	-1.385
C16–C17	0.260	0.162	0.059	-0.078	-0.019	-1.317
C15–O5	0.309	0.105	0.386	-0.745	-0.359	-1.932
C15–O6	0.412	-0.012	0.725	-1.453	-0.728	-2.004
C17–O7	0.412	-0.006	0.721	-1.444	-0.722	-2.002
C17–O8	0.303	0.109	0.369	-0.711	-0.342	-1.926
N3–H2	0.342	0.454	0.053	0.008	0.061	0.149
N3–H3	0.341	0.444	0.058	-0.004	0.053	-0.078
N4–H4	0.338	0.426	0.064	-0.022	0.042	-0.348
N5–H5	0.342	0.445	0.058	-0.005	0.053	-0.086
N6–H6	0.339	0.435	0.060	-0.011	0.049	-0.180
N6–H7	0.341	0.441	0.059	-0.009	0.051	-0.148
N7–H8	0.336	0.454	0.048	0.017	0.065	0.352
N8–H9	0.340	0.454	0.051	0.011	0.062	0.218
O5–H10	0.353	0.517	0.067	-0.004	0.062	-0.064
O8–H11	0.354	0.516	0.068	-0.007	0.061	-0.103
H6H7N6 … H8N7	0.022	-0.020	0.018	-0.041	-0.023	-2.274

Table S2. Continued.

	ρ(r)	∇^2 ρ(r)	G(r)	V(r)	H(r)	V(r)/G(r)
CP-RGD-1						
P–O1	0.217	-0.352	0.498	-1.084	-0.586	-2.176
P–O2	0.171	-0.188	0.301	-0.650	-0.348	-2.156
P–N1	0.181	-0.121	0.271	-0.573	-0.301	-2.111
P–N2	0.179	-0.127	0.272	-0.577	-0.304	-2.116
N1–H1	0.333	0.439	0.054	0.002	0.056	0.040
N1–C1	0.248	0.161	0.109	-0.177	-0.068	-1.630
N2–C4	0.253	0.173	0.123	-0.202	-0.079	-1.648
N2–C5	0.255	0.171	0.123	-0.203	-0.080	-1.652
C1–C2	0.249	0.146	0.056	-0.075	-0.019	-1.345
C2–C3	0.255	0.153	0.057	-0.077	-0.019	-1.335
O2–C3	0.225	0.094	0.196	-0.369	-0.173	-1.881
C–Cl1	0.166	0.044	0.055	-0.099	-0.044	-1.799
C–Cl2	0.166	0.044	0.055	-0.099	-0.044	-1.800
O1...H9(RGD)	0.032	-0.024	0.024	-0.054	-0.030	-2.252
C6–N3	0.313	0.271	0.165	-0.262	-0.097	-1.588
C6–N4	0.384	0.335	0.299	-0.514	-0.215	-1.719
C6–N5	0.199	0.267	0.199	-0.332	-0.133	-1.666
N5–C7	0.262	0.187	0.131	-0.215	-0.084	-1.641
C7–C8	0.247	0.144	0.055	-0.075	-0.020	-1.353
C9–C10	0.242	0.138	0.055	-0.075	-0.020	-1.370
N6–C10	0.266	0.183	0.104	-0.162	-0.058	-1.560
C11–O3	0.393	0.040	0.637	-1.264	-0.627	-1.984
C11–N7	0.328	0.233	0.298	-0.537	-0.239	-1.804
C12–N7	0.271	0.200	0.136	-0.221	-0.085	-1.631
O4–C13	0.394	0.035	0.643	-1.278	-0.634	-1.987
C13–N8	0.330	0.257	0.267	-0.470	-0.203	-1.759
C14–N8	0.264	0.186	0.125	-0.203	-0.078	-1.627
C14–C15	0.255	0.158	0.055	-0.071	-0.016	-1.288
C14–C16	0.248	0.144	0.055	-0.073	-0.019	-1.341
C16–C17	0.261	0.164	0.060	-0.080	-0.020	-1.323
C15–O5	0.309	0.105	0.386	-0.746	-0.360	-1.932
C15–O6	0.408	-0.010	0.713	-1.429	-0.716	-2.004
C17–O7	0.411	-0.004	0.716	-1.432	-0.717	-2.001
C17–O8	0.305	0.111	0.370	-0.712	-0.342	-1.925
N3–H2	0.342	0.454	0.053	0.008	0.061	0.146
N3–H3	0.341	0.444	0.058	-0.004	0.053	-0.078
N4–H4	0.338	0.426	0.064	-0.022	0.042	-0.345
N5–H5	0.342	0.445	0.058	-0.005	0.053	-0.088
N6–H6	0.341	0.436	0.062	-0.014	0.047	-0.234
N6–H7	0.340	0.436	0.060	-0.011	0.049	-0.191
N7–H8	0.340	0.454	0.051	0.011	0.062	0.216

N8–H9	0.325	0.434	0.047	0.014	0.061	0.290
O5–H10	0.354	0.514	0.068	-0.007	0.061	-0.102
O8–H11	0.354	0.516	0.068	-0.007	0.061	-0.096
Cl1CH … HCCl2	0.006	-0.006	0.004	-0.010	-0.006	-2.334
O2 … HCCl2	0.006	-0.006	0.005	-0.011	-0.006	-2.303
N7H8 … O4C13	0.020	-0.020	0.018	-0.042	-0.023	-2.276
C15O6 … N1H1	0.016	-0.013	0.012	-0.028	-0.016	-2.256
C16H … C4H	0.003	-0.003	0.002	-0.004	-0.003	-2.349

Table S2. Continued.

	ρ(r)	∇^2 ρ(r)	G(r)	V(r)	H(r)	V(r)/G(r)
CP-RGD-6						
P–O1	0.219	-0.359	0.508	-1.106	-0.598	-2.176
P–O2	0.168	-0.185	0.296	-0.637	-0.342	-2.156
P–N1	0.187	-0.138	0.293	-0.621	-0.328	-2.117
P–N2	0.172	-0.101	0.243	-0.511	-0.268	-2.104
N1–H1	0.311	0.407	0.050	0.001	0.051	0.023
N1–C1	0.253	0.165	0.106	-0.170	-0.064	-1.610
N2–C4	0.254	0.167	0.110	-0.178	-0.068	-1.619
N2–C5	0.255	0.170	0.114	-0.185	-0.071	-1.625
C1–C2	0.247	0.143	0.055	-0.075	-0.020	-1.356
C2–C3	0.253	0.150	0.057	-0.076	-0.019	-1.341
O2–C3	0.226	0.103	0.185	-0.343	-0.159	-1.860
C–Cl1	0.165	0.044	0.055	-0.099	-0.044	-1.800
C–Cl2	0.055	0.045	0.055	-0.099	-0.044	-1.796
O1...H2(RGD)	0.024	-0.017	0.017	-0.039	-0.021	-2.243
C6–N3	0.322	0.284	0.166	-0.260	-0.095	-1.572
C6–N4	0.377	0.333	0.286	-0.489	-0.203	-1.708
C6–N5	0.318	0.271	0.198	-0.327	-0.130	-1.657
N5–C7	0.262	0.187	0.130	-0.213	-0.083	-1.641
C7–C8	0.247	0.144	0.056	-0.076	-0.020	-1.355
C9–C10	0.242	0.137	0.054	-0.075	-0.020	-1.372
N6–C10	0.270	0.186	0.105	-0.164	-0.058	-1.557
C11–O3	0.391	0.040	0.632	-1.254	-0.622	-1.984
C11–N7	0.328	0.229	0.303	-0.548	-0.245	-1.811
C12–N7	0.272	0.201	0.130	-0.210	-0.080	-1.614
O4–C13	0.397	0.029	0.654	-1.301	-0.647	-1.989
C13–N8	0.326	0.250	0.267	-0.471	-0.204	-1.765
C14–N8	0.264	0.187	0.142	-0.237	-0.095	-1.670
C14–C15	0.254	0.156	0.055	-0.072	-0.016	-1.297
C14–C16	0.246	0.142	0.055	-0.074	-0.019	-1.349
C16–C17	0.261	0.163	0.059	-0.077	-0.018	-1.309
C15–O5	0.307	0.105	0.381	-0.736	-0.355	-1.931
C15–O6	0.412	-0.013	0.727	-1.458	-0.730	-2.004
C17–O7	0.412	-0.004	0.718	-1.438	-0.720	-2.001
C17–O8	0.304	0.112	0.368	-0.708	-0.340	-1.923
N3–H2	0.331	0.446	0.047	0.017	0.064	0.372
N3–H3	0.342	0.446	0.057	-0.003	0.054	-0.058
N4–H4	0.339	0.427	0.064	-0.022	0.042	-0.346
N5–H5	0.342	0.447	0.057	-0.003	0.055	-0.046
N6–H6	0.339	0.440	0.057	-0.005	0.053	-0.086
N6–H7	0.340	0.436	0.060	-0.011	0.049	-0.189
N7–H8	0.339	0.455	0.051	0.012	0.063	0.236
N8–H9	0.342	0.451	0.054	0.005	0.059	0.094

O5–H10	0.354	0.517	0.068	-0.005	0.062	-0.082
O8–H11	0.354	0.516	0.068	-0.006	0.061	-0.092
C1H … HCCl1	0.006	-0.005	0.004	-0.010	-0.005	-2.331
C3H … HCCl2	0.003	-0.002	0.002	-0.004	-0.002	-2.336
N1 … HCCl1	0.007	-0.006	0.005	-0.011	-0.006	-2.295
Cl1CH … HCCl2	0.005	-0.005	0.004	-0.009	-0.005	-2.334
N1H1 … N4	0.034	-0.020	0.021	-0.047	-0.026	-2.239
N7H8 … O4C13	0.020	-0.020	0.018	-0.041	-0.023	-2.278

Table S2. Continued.

	ρ(r)	∇^2 ρ(r)	G(r)	V(r)	H(r)	V(r)/G(r)
CP-RGD-7						
P–O1	0.215	-0.345	0.490	-1.067	-0.576	-2.176
P–O2	0.172	-0.196	0.309	-0.668	-0.358	-2.158
P–N1	0.187	-0.135	0.291	-0.615	-0.325	-2.116
P–N2	0.176	-0.110	0.256	-0.540	-0.284	-2.107
N1–H1	0.328	0.434	0.051	0.006	0.057	0.111
N1–C1	0.250	0.162	0.108	-0.176	-0.068	-1.625
N2–C4	0.252	0.165	0.111	-0.181	-0.070	-1.629
N2–C5	0.253	0.168	0.115	-0.189	-0.073	-1.637
C1–C2	0.248	0.143	0.055	-0.075	-0.020	-1.355
C2–C3	0.253	0.151	0.057	-0.077	-0.019	-1.341
O2–C3	0.222	0.096	0.184	-0.344	-0.160	-1.869
C–Cl1	0.167	0.045	0.055	-0.099	-0.044	-1.797
C–Cl2	0.168	0.046	0.055	-0.099	-0.044	-1.793
O1...H10(RGD)	0.059	-0.040	0.045	-0.101	-0.055	-2.221
C6–N3	0.312	0.271	0.165	-0.262	-0.097	-1.588
C6–N4	0.384	0.336	0.299	-0.514	-0.215	-1.719
C6–N5	0.316	0.267	0.199	-0.332	-0.133	-1.665
N5–C7	0.262	0.187	0.131	-0.214	-0.084	-1.642
C7–C8	0.247	0.144	0.055	-0.075	-0.020	-1.352
C9–C10	0.245	0.141	0.055	-0.076	-0.020	-1.365
N6–C10	0.264	0.179	0.102	-0.160	-0.057	-1.563
C11–O3	0.394	0.038	0.639	-1.269	-0.630	-1.985
C11–N7	0.327	0.229	0.301	-0.544	-0.243	-1.809
C12–N7	0.272	0.201	0.132	-0.213	-0.081	-1.618
O4–C13	0.396	0.031	0.650	-1.292	-0.642	-1.988
C13–N8	0.328	0.251	0.271	-0.478	-0.208	-1.768
C14–N8	0.265	0.188	0.142	-0.237	-0.095	-1.669
C14–C15	0.255	0.156	0.054	-0.070	-0.015	-1.285
C14–C16	0.242	0.137	0.054	-0.074	-0.020	-1.369
C16–C17	0.260	0.163	0.0589	-0.077	-0.018	-1.307
C15–O5	0.327	0.104	0.427	-0.827	-0.401	-1.939
C15–O6	0.401	0.006	0.682	-1.363	-0.681	-1.998
C17–O7	0.412	-0.002	0.717	-1.435	-0.718	-2.001
C17–O8	0.302	0.110	0.364	-0.701	-0.337	-1.924
N3–H2	0.342	0.454	0.053	0.008	0.060	0.145
N3–H3	0.341	0.444	0.058	-0.004	0.053	-0.078
N4–H4	0.338	0.426	0.064	-0.022	0.042	-0.348
N5–H5	0.342	0.445	0.058	-0.005	0.053	-0.081
N6–H6	0.340	0.435	0.061	-0.013	0.048	-0.215
N6–H7	0.340	0.436	0.060	-0.012	0.049	-0.193
N7–H8	0.340	0.454	0.051	0.012	0.063	0.229

N8–H9	0.342	0.453	0.053	0.006	0.060	0.119
O5–H10	0.300	0.412	0.068	-0.033	0.035	-0.484
O8–H11	0.355	0.516	0.068	-0.007	0.061	-0.108
C1H … HCCl1	0.005	-0.005	0.004	-0.009	-0.005	-2.332
N1 … HCCl1	0.007	-0.006	0.005	-0.011	-0.006	-2.296
Cl1CH … HCCl2	0.005	-0.005	0.004	-0.010	-0.005	-2.335
N1H1 … O6	0.022	-0.016	0.016	-0.037	-0.020	-2.245
N7H8 … O4C13	0.019	-0.020	0.018	-0.041	-0.023	-2.279

Table S2. Continued.

	ρ(r)	∇^2 ρ(r)	G(r)	V(r)	H(r)	V(r)/G(r)
CP-RGD-8						
P–O1	0.216	-0.347	0.492	-1.072	-0.579	-2.176
P–O2	0.171	-0.190	0.303	-0.654	-0.350	-2.156
P–N1	0.187	-0.138	0.294	-0.622	-0.328	-2.118
P–N2	0.176	-0.115	0.260	-0.548	-0.288	-2.111
N1–H1	0.327	0.433	0.051	0.006	0.057	0.122
N1–C1	0.250	0.163	0.109	-0.177	-0.068	-1.624
N2–C4	0.253	0.168	0.119	-0.196	-0.078	-1.647
N2–C5	0.254	0.169	0.119	-0.195	-0.077	-1.644
C1–C2	0.247	0.143	0.055	-0.075	-0.020	-1.355
C2–C3	0.252	0.149	0.057	-0.076	-0.019	-1.342
O2–C3	0.224	0.099	0.183	-0.341	-0.158	-1.864
C–Cl1	0.166	0.045	0.055	-0.100	-0.044	-1.798
C–Cl2	0.166	0.044	0.055	-0.100	-0.044	-1.799
O1...H11(RGD)	0.055	-0.039	0.042	-0.094	-0.052	-2.231
C6–N3	0.312	0.271	0.165	-0.262	-0.097	-1.588
C6–N4	0.384	0.336	0.299	-0.514	-0.215	-1.719
C6–N5	0.316	0.267	0.199	-0.331	-0.132	-1.664
N5–C7	0.262	0.187	0.131	-0.214	-0.084	-1.642
C7–C8	0.247	0.144	0.05	-0.075	-0.019	-1.351
C9–C10	0.245	0.141	0.055	-0.076	-0.020	-1.364
N6–C10	0.264	0.178	0.102	-0.160	-0.058	-1.563
C11–O3	0.394	0.038	0.639	-1.270	-0.630	-1.985
C11–N7	0.327	0.229	0.302	-0.544	-0.243	-1.810
C12–N7	0.272	0.202	0.131	-0.212	-0.081	-1.616
O4–C13	0.397	0.030	0.653	-1.299	-0.646	-1.989
C13–N8	0.327	0.251	0.268	-0.473	-0.205	-1.766
C14–N8	0.264	0.187	0.143	-0.238	-0.096	-1.673
C14–C15	0.254	0.155	0.055	-0.072	-0.017	-1.301
C14–C16	0.245	0.140	0.055	-0.075	-0.020	-1.363
C16–C17	0.260	0.162	0.057	-0.074	-0.017	-1.291
C15–O5	0.306	0.104	0.381	-0.735	-0.355	-1.932
C15–O6	0.413	-0.012	0.726	-1.456	-0.729	-2.004
C17–O7	0.401	0.013	0.677	-1.351	-0.674	-1.995
C17–O8	0.321	0.111	0.407	-0.787	-0.380	-1.932
N3–H2	0.342	0.454	0.053	0.008	0.061	0.1454
N3–H3	0.341	0.444	0.058	-0.004	0.053	-0.078
N4–H4	0.338	0.426	0.064	-0.022	0.042	-0.345
N5–H5	0.342	0.445	0.058	-0.005	0.053	-0.08
N6–H6	0.340	0.435	0.061	-0.013	0.048	-0.213
N6–H7	0.340	0.436	0.060	-0.012	0.049	-0.195
N7–H8	0.339	0.454	0.051	0.012	0.063	0.230
N8–H9	0.342	0.452	0.054	0.005	0.059	0.090

O5–H10	0.354	0.516	0.067	-0.006	0.062	-0.088
O8–H11	0.306	0.427	0.067	-0.028	0.039	-0.411
Cl1CH … HCCl2	0.007	-0.006	0.005	-0.011	-0.006	-2.329
N1H1 … O7	0.023	-0.016	0.017	-0.038	-0.021	-2.244
N7H8 … O4C13	0.019	-0.020	0.018	-0.041	-0.023	-2.279

Table S2. Continued.

	ρ(r)	∇^2 ρ(r)	G(r)	V(r)	H(r)	V(r)/G(r)
CP-RGD-10						
P–O1	0.218	-0.357	0.505	-1.100	-0.595	-2.177
P–O2	0.170	-0.184	0.297	-0.640	-0.343	-2.155
P–N1	0.186	-0.135	0.290	-0.613	-0.324	-2.117
P–N2	0.175	-0.112	0.255	-0.539	-0.283	-2.110
N1–H1	0.329	0.437	0.051	0.007	0.058	0.142
N1–C1	0.250	0.163	0.109	-0.176	-0.068	-1.625
N2–C4	0.254	0.170	0.117	-0.192	-0.075	-1.638
N2–C5	0.254	0.170	0.114	-0.186	-0.072	-1.629
C1–C2	0.248	0.143	0.055	-0.075	-0.020	-1.355
C2–C3	0.253	0.150	0.057	-0.076	-0.019	-1.340
O2–C3	0.225	0.101	0.187	-0.348	-0.161	-1.866
C–Cl1	0.166	0.045	0.055	-0.100	-0.044	-1.798
C–Cl2	0.167	0.045	0.055	-0.099	-0.044	-1.796
H1...O6(RGD)	0.021	-0.017	0.017	-0.037	-0.021	-2.258
C6–N3	0.292	0.235	0.136	-0.213	-0.077	-1.567
C6–N4	0.385	0.338	0.302	-0.520	-0.218	-1.720
C6–N5	0.330	0.281	0.227	-0.383	-0.157	-1.690
N5–C7	0.262	0.188	0.140	-0.233	-0.093	-1.665
C7–C8	0.244	0.140	0.055	-0.074	-0.020	-1.361
C9–C10	0.238	0.133	0.054	-0.075	-0.021	-1.389
N6–C10	0.266	0.186	0.107	-0.168	-0.060	-1.565
C11–O3	0.393	0.046	0.633	-1.254	-0.621	-1.981
C11–N7	0.317	0.246	0.244	-0.426	-0.182	-1.747
C12–N7	0.258	0.179	0.144	-0.243	-0.099	-1.689
O4–C13	0.397	0.040	0.646	-1.281	-0.635	-1.984
C13–N8	0.324	0.242	0.273	-0.486	-0.213	-1.779
C14–N8	0.261	0.182	0.135	-0.225	-0.090	-1.664
C14–C15	0.255	0.157	0.054	-0.068	-0.014	-1.269
C14–C16	0.249	0.145	0.0547	-0.073	-0.018	-1.337
C16–C17	0.261	0.164	0.060	-0.080	-0.020	-1.324
C15–O5	0.324	0.107	0.416	-0.806	-0.389	-1.935
C15–O6	0.401	-0.006	0.693	-1.387	-0.694	-2.002
C17–O7	0.411	-0.004	0.717	-1.434	-0.718	-2.001
C17–O8	0.303	0.109	0.368	-0.709	-0.340	-1.926
N3–H2	0.340	0.445	0.055	0.001	0.056	0.020
N3–H3	0.332	0.442	0.050	0.011	0.061	0.215
N4–H4	0.337	0.423	0.064	-0.023	0.041	-0.362
N5–H5	0.339	0.453	0.051	0.010	0.062	0.199
N6–H6	0.339	0.437	0.059	-0.009	0.050	-0.149
N6–H7	0.340	0.435	0.060	-0.012	0.048	-0.199
N7–H8	0.341	0.450	0.053	0.007	0.059	0.106

N8–H9	0.342	0.453	0.053	0.006	0.060	0.118
O5–H10	0.305	0.411	0.070	-0.037	0.033	-0.527
O8–H11	0.354	0.515	0.068	-0.008	0.061	-0.111
C3H … HCCl2	0.005	-0.005	0.004	-0.009	-0.005	-2.331
O1 … H3N3	0.022	-0.017	0.017	-0.039	-0.022	-2.247
O1 … H5N5	0.020	-0.015	0.015	-0.035	-0.019	-2.248
C8H … H9N8	0.003	-0.002	0.002	-0.004	-0.002	-2.337
N6 … HC12	0.024	-0.017	0.017	-0.038	-0.021	-2.254
N7 … H9N8	0.016	-0.016	0.013	-0.031	-0.017	-2.290
N3 … H10O5	0.050	-0.024	0.030	-0.065	-0.036	-2.206

Table S3.

The average kinetic, potential and non-bond energies (kcal/mol) measured for the CP-RGD-PEG systems.

System	Kinetic energy	Potential energy	Non-bond energy
CP-RGD	1285	-2909	-2925
CP-RGD-1PEG	1411	-2886	-2891
CP-RGD-2PEG	1537	-2848	-2857
CP-RGD-3PEG	1663	-2796	-2812
CP-RGD-4PEG	1789	-2761	-2786
CP-RGD-5PEG	1916	-2726	-2742
CP-RGD-6PEG	2042	-2667	-2682
CP-RGD-7PEG	2168	-2632	-2653
CP-RGD-8PEG	2294	-2623	-2651
CP-RGD-9PEG	2420	-2555	-2586
CP-RGD-10PEG	2547	-2528	-2554