Supporting Materials

Table S1. Binding free energy contributions of the key binding-site residues calculated from the binding energy decomposition for CXCR4 (kcal/mol)

	CXCR4				
	ΔE_{vdw}	ΔE_{ele}	ΔG_{GB}	ΔG_{SA}	ΔG_{bind}
Ile4	-8.26	0.02	0.16	-1.46	-9.54
Thr8	-6.26	-2.12	3.06	-1.2	-6.52
Glu14	-0.86	-63.02	60.14	-0.88	-4.62
Met16	-5.58	-3.26	3.36	-0.94	-6.42
Asp20	-0.50	-66.90	61.44	-0.54	-6.50
Tyr21	-7.98	0.50	0.28	-1.54	-8.74
Asp22	-1.38	-43.96	42.36	-0.18	-3.16
Glu26	-2.30	-55.86	54.06	-0.64	-4.72
Pro27	-11.02	-0.44	1.16	-1.60	-11.90
Cys28	-6.70	-1.02	1.02	-0.92	-7.60
Arg30	-2.20	53.82	-50.26	-0.46	0.90
Glu32	0.20	-59.34	56.48	-0.40	-3.08
Tyr116	-5.72	0.40	-0.18	-0.52	-6.02
Asp187	0.14	-61.14	57.36	-0.70	-4.36
Asp262	0.42	-57.66	54.74	-0.60	-3.10
Cys274	-6.56	-0.44	0.68	-0.74	-7.06
Glu277	-3.60	-56.32	53.58	-1.00	-7.34
Glu288	-3.10	-53.74	52.18	-0.88	-5.56

Table S2. Binding free energy contributions of the key binding-site residues calculated from the binding energy decomposition for CXCL12(kcal/mol)

	CXCL12				
	ΔE_{vdw}	ΔE_{ele}	ΔG_{GB}	ΔG_{SA}	ΔG_{bind}
Lys1	-4.72	-91.48	91.28	-2.00	-6.92
Val3	-13.82	-3.42	3.44	-2.38	-16.16
Ala35	-4.78	-99.78	145.18	-3.22	19.84
Gln37	-16.20	-27.84	2.68	-2.22	-30.28
Val39	-15.40	-2.86	3.26	-2.78	-25.14
Arg41	-18.34	-84.46	-3.62	-2.02	-89.94
Asn44	6.60	-38.42	-5.92	1.18	-41.06
Arg47	-11.34	-62.86	-26.84	-0.78	-84.36
Ile58	-4.92	-63.04	71.34	-2.22	-3.80
Gln59	-2.44	-32.54	1.42	-0.98	-55.36
Tyr61	-6.66	-61.88	61.42	-1.76	-8.60

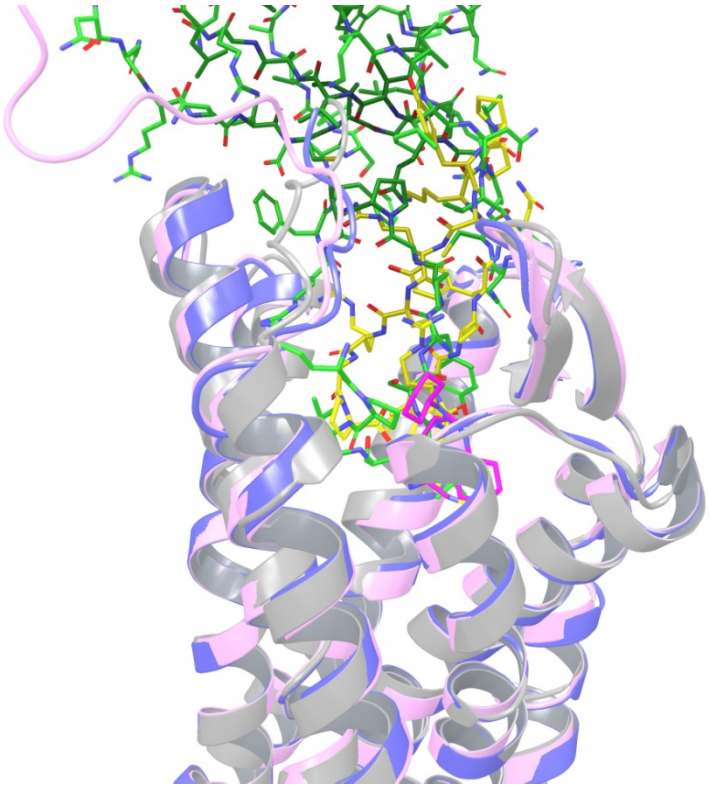

Figure S1. CXCR4-CXCL12 binding modes in comparison with small molecule IT1t and cyclic peptide CVX15 in the CXCR4 crystal structures. Carbon atoms of CXCL12 are colored in green, carbon atoms of IT1t colored in magenta, and carbon atoms of CVX12 colored in yellow.

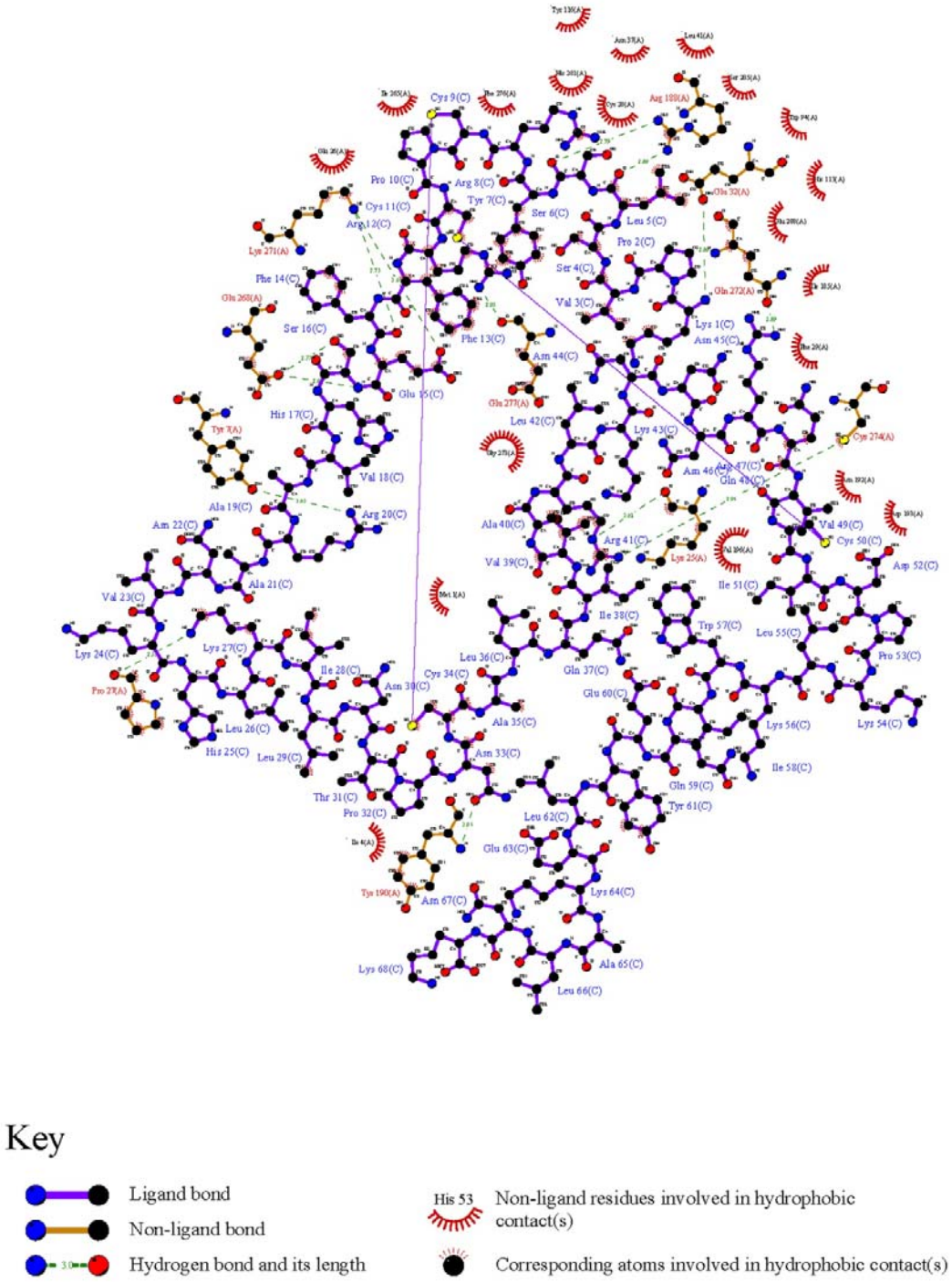

Figure S2. Schematic depiction of the major interactions of the CXCR4-CXCL12 complex predicted by protein-protein docking (generated by the LIGPLOT program[1]).

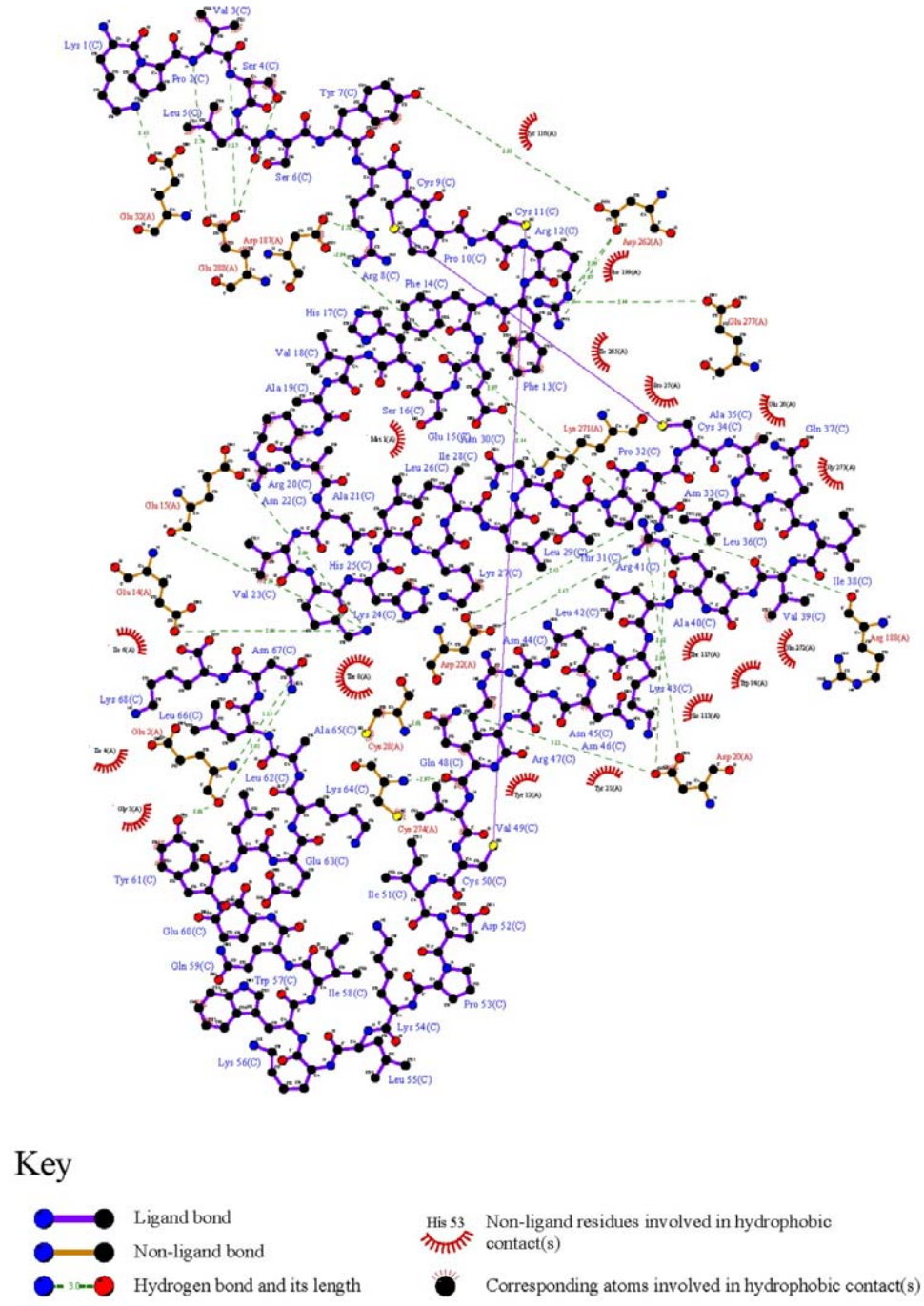

Figure S3. Schematic depiction of major interactions of the CXCR4-CXCL12 averaged structure over the last 30 ns MD trajectory (generated by the LIGPLOT program[1]).

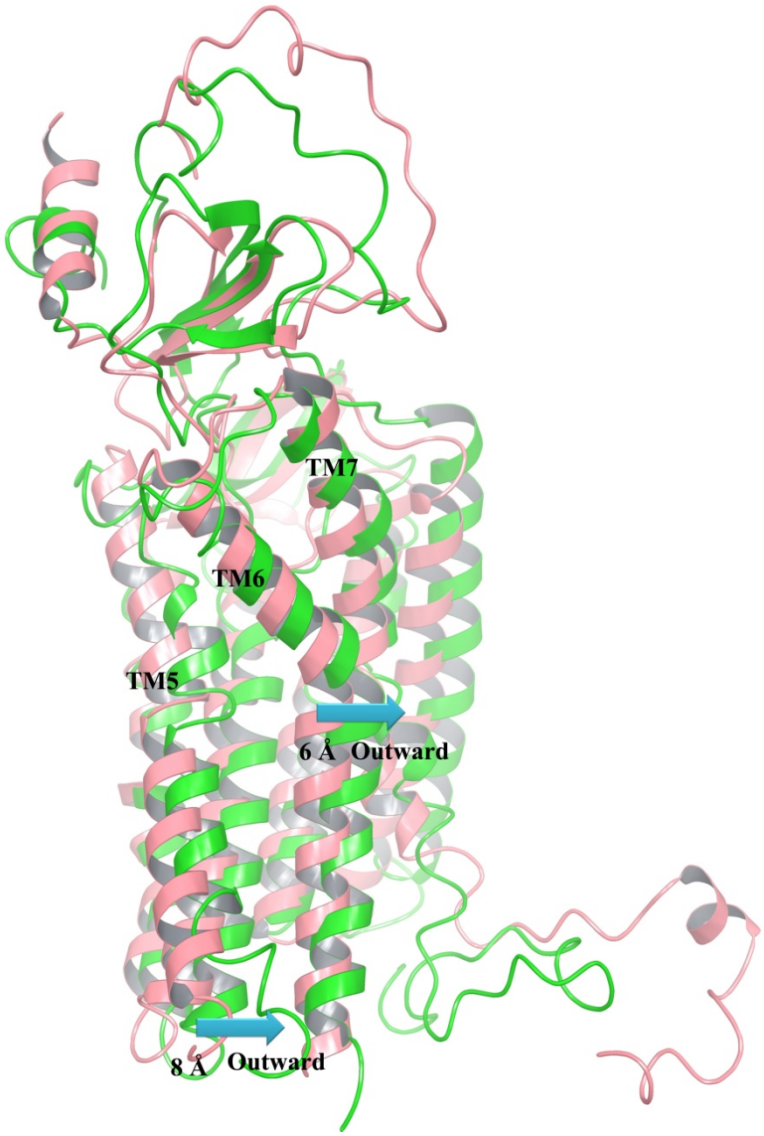

Figure S4. Comparison of the complex structure predicted by protein-protein docking (ribbon colored in pink) and the averaged conformation over the last 30 ns MD trajectory (ribbon colored in green). The arrow indicates the movement of TM5 and TM6.

References

1. Wallace, A. C.; Laskowski, R. A.; Thornton, J. M. LIGPLOT: a program to generate schematic diagrams of protein-ligand interactions. *Protein Eng.* **1995,** 8, 127-134.