

Table S7. The binding free energies (ΔG) in kcal/mol at (TLR4-MD2)/(TLR4*-MD2*) interface computed by both molecular mechanics generalized Born surface area (MM-GBSA) and molecular mechanics Poisson-Boltzmann surface area (MM-PBSA) methods. The free energies in each trajectory of the ligand-free (TLR4-MD2)₂ tetramer, lipopolysaccharide (LPS)-bound (TLR4-MD2)₂ tetramer, and neoseptin3-bound (TLR4-MD2)₂ tetramer complexes are averaged over the 1000 frames from the last 1.0 μ s of that trajectory with an interval of 1.0 ns. Trajectories in each complex are identified with a number from 1 to 4 (#) and their average is denoted by '1-4' as shaded in light grey. A negative value is a favorable free energy, while a positive value is an unfavorable. The values in parenthesis are standard deviation. ΔE_{MM} is molecular mechanics free energy which is divided into ΔE_{ele} and ΔE_{vdw} representing the contributions from the electrostatic and van der Waals interactions, respectively. ΔG_{sol} is solvation free energy expressed by ΔG_{pol} and ΔG_{nonpol} , the polar and non-polar contributions, respectively.

Complex	#	ΔE_{MM}				Generalized Born (GB)		Poisson-Boltzmann (PB)		ΔG
		ΔE_{MM}		ΔG_{sol}		ΔG	ΔG_{sol}			
		ΔE_{ele}	ΔE_{vdw}	ΔG_{pol}	ΔG_{nonpol}		ΔG_{pol}	ΔG_{nonpol}		
(TLR4-MD2) ₂	1	-275.67 (87.78)	-137.58 (13.02)	375.87 (82.49)	-20.87 (1.87)	-58.23 (12.75)	329.77 (83.66)	-19.08 (1.46)	-102.53 (15.47)	
(TLR4-MD2) ₂	2	-266.19 (66.36)	-161.13 (16.63)	373.78 (63.72)	-23.18 (2.19)	-76.69 (16.56)	331.21 (64.32)	-20.58 (1.59)	-116.66 (18.43)	
(TLR4-MD2) ₂	3	-210.04 (67.62)	-104.15 (12.85)	280.08 (62.66)	-15.41 (1.53)	-49.49 (10.95)	234.22 (62.54)	-13.98 (1.22)	-93.93 (12.46)	
(TLR4-MD2) ₂	4	-363.99 (80.16)	-138.18 (16.62)	451.11 (80.24)	-20.70 (2.63)	-71.74 (15.23)	413.22 (80.41)	-17.87 (2.02)	-106.81 (18.80)	
(TLR4-MD2) ₂	1-4	-278.97 (63.65)	-135.26 (23.46)	370.21 (70.03)	-20.04 (3.29)	-64.04 (12.45)	327.11 (73.18)	-17.88 (2.82)	-104.98 (9.45)	
(TLR4-MD2-LPS) ₂	1	10.39 (65.89)	-219.44 (13.95)	161.32 (65.97)	-28.00 (2.15)	-75.70 (13.19)	132.10 (64.93)	-23.33 (1.44)	-100.26 (17.71)	
(TLR4-MD2-LPS) ₂	2	-42.30 (66.60)	-216.60 (15.04)	213.07 (65.54)	-28.87 (2.24)	-74.69 (14.94)	180.66 (66.48)	-24.18 (1.35)	-102.41 (17.18)	
(TLR4-MD2-LPS) ₂	3	-162.23 (76.06)	-206.31 (13.59)	300.12 (72.08)	-27.99 (1.86)	-96.38 (15.33)	256.23 (72.21)	-23.78 (1.14)	-136.06 (18.09)	
(TLR4-MD2-LPS) ₂	4	-191.27 (61.00)	-226.94 (15.91)	333.83 (58.23)	-31.37 (2.25)	-115.73 (17.74)	289.68 (57.84)	-25.63 (1.43)	-154.13 (19.93)	
(TLR4-MD2-LPS) ₂	1-4	-96.35 (96.03)	-217.32 (8.54)	252.09 (79.06)	-29.06 (1.60)	-90.63 (19.49)	214.67 (71.48)	-24.23 (1.00)	-123.22 (26.33)	
(TLR4-MD2-neoseptin3) ₂	1	-62.70 (68.23)	-215.18 (14.21)	208.91 (65.78)	-27.52 (2.03)	-96.47 (16.15)	156.79 (65.90)	-23.13 (1.40)	-144.20 (18.90)	
(TLR4-MD2-neoseptin3) ₂	2	-132.96 (87.76)	-243.85 (17.00)	287.41 (84.77)	-33.16 (2.35)	-122.54 (18.54)	241.70 (86.50)	-26.28 (1.24)	-161.37 (20.97)	
(TLR4-MD2-neoseptin3) ₂	3	-9.33 (51.50)	-245.55 (12.83)	176.50 (75.18)	-31.62 (2.05)	-109.99 (14.73)	131.95 (75.23)	-25.30 (1.37)	-148.21 (17.26)	
(TLR4-MD2-neoseptin3) ₂	4	31.28 (84.48)	-233.09 (14.66)	136.04 (83.64)	-30.19 (2.24)	-95.94 (16.85)	98.25 (81.98)	-24.42 (1.51)	-127.97 (17.76)	
(TLR4-MD2-neoseptin3) ₂	1-4	-43.43 (71.02)	-234.42 (13.96)	202.22 (64.14)	-30.62 (2.40)	-106.24 (12.67)	157.17 (61.25)	-24.78 (1.34)	-145.44 (13.76)	