

Table S2. The binding free energies (ΔG) in kcal/mol computed by both molecular mechanics generalized Born surface area (MM-GBSA) and molecular mechanics Poisson-Boltzmann surface area (MM-PBSA) methods at TLR4/MD2 interface. The free energies in each trajectory of the ligand-free TLR4-MD2 heterodimer, (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	#	Generalized Born (GB)				Poisson-Boltzmann (PB)			
		ΔE_{MM}		ΔG_{sol}		ΔG	ΔG_{sol}		ΔG
		ΔE_{ele}	ΔE_{vdw}	ΔG_{pol}	ΔG_{nonpol}		ΔG_{pol}	ΔG_{nonpol}	
(TLR4-MD2)	1	-572.05 (95.42)	-120.39 (19.61)	596.19 (91.54)	-18.94 (3.00)	-115.18 (23.28)	581.69 (89.98)	-13.99 (2.19)	-124.72 (24.91)
(TLR4-MD2)	2	-598.90 (69.11)	-133.64 (20.06)	630.65 (69.34)	-21.43 (2.85)	-123.30 (18.13)	619.65 (67.95)	-15.90 (2.19)	-128.77 (21.54)
(TLR4-MD2)	3	-627.92 (81.63)	-133.93 (19.24)	659.51 (78.25)	-21.39 (2.72)	-123.70 (17.54)	653.30 (75.74)	-15.53 (2.07)	-124.05 (24.31)
(TLR4-MD2)	4	-621.46 (72.95)	-121.36 (16.72)	659.01 (70.49)	-18.94 (2.26)	-102.73 (16.11)	636.84 (70.64)	-14.53 (1.63)	-120.49 (17.24)
(TLR4-MD2)	1-4	-605.08 (25.29)	-127.33 (7.47)	636.34 (29.97)	-20.18 (1.43)	-116.23 (9.82)	622.87 (30.70)	-14.99 (0.88)	-124.51 (3.39)
(TLR4-MD2) ₂	1	-570.87 (61.76)	-105.06 (7.92)	585.02 (56.18)	-17.06 (1.16)	-107.94 (13.48)	573.90 (56.03)	-12.14 (0.67)	-114.16 (13.64)
(TLR4-MD2) ₂	2	-603.81 (49.14)	-104.56 (7.44)	614.77 (46.09)	-16.99 (0.80)	-110.56 (9.92)	611.77 (45.86)	-11.99 (0.50)	-108.57 (14.24)
(TLR4-MD2) ₂	3	-603.33 (52.31)	-104.74 (7.32)	616.09 (47.24)	-17.00 (0.80)	-108.97 (10.97)	606.66 (48.18)	-11.86 (0.47)	-113.26 (14.01)
(TLR4-MD2) ₂	4	-528.91 (53.16)	-98.78 (7.00)	557.60 (48.32)	-15.57 (0.86)	-85.65 (10.09)	538.99 (48.41)	-11.57 (0.56)	-100.25 (11.62)
(TLR4-MD2) ₂	1-4	-576.73 (35.41)	-103.29 (3.01)	593.37 (27.83)	-16.66 (0.72)	-103.28 (11.80)	582.83 (33.70)	-11.89 (0.24)	-109.06 (6.36)
(TLR4-MD2-LPS) ₂	1	-583.45 (60.07)	-115.06 (7.63)	613.32 (54.60)	-18.37 (0.86)	-103.55 (12.97)	605.31 (56.37)	-13.05 (0.61)	-106.23 (17.36)
(TLR4-MD2-LPS) ₂	2	-567.83 (52.53)	-113.85 (8.15)	597.25 (48.96)	-18.11 (0.98)	-102.52 (13.25)	585.46 (49.95)	-12.95 (0.59)	-109.16 (12.96)
(TLR4-MD2-LPS) ₂	3	-569.64 (50.69)	-114.58 (7.86)	601.61 (46.93)	-18.31 (1.02)	-100.91 (10.51)	590.64 (47.36)	-13.10 (0.55)	-106.68 (11.89)
(TLR4-MD2-LPS) ₂	4	-606.82 (55.32)	-120.51 (7.71)	628.82 (51.76)	-19.46 (0.79)	-117.94 (11.82)	622.40 (51.41)	-13.63 (0.42)	-118.54 (14.02)
(TLR4-MD2-LPS) ₂	1-4	-581.94 (18.00)	-116.00 (3.05)	610.25 (14.12)	-18.56 (0.61)	-106.23 (7.88)	600.95 (16.59)	-13.18 (0.30)	-110.15 (5.74)

(TLR4-MD2-neoseptin3) ₂	1	-464.97 (48.56)	-112.56 (6.99)	487.82 (41.54)	-17.09 (0.86)	-106.78 (14.69)	475.44 (42.41)	-11.74 (0.51)	-113.81 (16.58)
(TLR4-MD2-neoseptin3) ₂	2	-482.94 (45.91)	-105.82 (6.93)	507.38 (42.09)	-16.75 (0.70)	-98.12 (9.33)	493.49 (41.75)	-11.65 (0.39)	-106.90 (11.51)
(TLR4-MD2-neoseptin3) ₂	3	-522.16 (48.58)	-107.03 (7.04)	546.06 (45.23)	-16.82 (0.73)	-99.94 (9.63)	531.81 (44.82)	-11.77 (0.49)	-109.14 (12.53)
(TLR4-MD2-neoseptin3) ₂	4	-458.30 (51.86)	-107.49 (6.97)	481.73 (44.78)	-16.50 (0.68)	-100.54 (13.12)	464.92 (43.94)	-11.57 (0.38)	-112.42 (16.61)
(TLR4-MD2-neoseptin3) ₂	1-4	-482.09 (28.67)	-108.23 (2.97)	505.75 (29.02)	-16.79 (0.24)	-101.35 (3.77)	491.42 (29.40)	-11.68 (0.09)	-110.57 (3.13)