

**Table S3.** The binding free energies ( $\Delta G$ ) 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.

Complex	#	$\Delta E_{MM}$		Generalized Born (GB)			Poisson-Boltzmann (PB)		
		$\Delta E_{ele}$	$\Delta E_{vdw}$	$\Delta G_{sol}$		$\Delta G$	$\Delta G_{sol}$		$\Delta G$
				$\Delta G_{pol}$	$\Delta G_{nonpol}$		$\Delta G_{pol}$	$\Delta G_{nonpol}$	
(TLR4-MD2) <sub>2</sub>	1	<b>-401.86</b> (49.13)	<b>-96.31</b> (6.34)	<b>433.13</b> (45.34)	<b>-14.79</b> (0.77)	<b>-79.82</b> (9.34)	<b>415.09</b> (44.74)	<b>-11.18</b> (0.47)	<b>-94.25</b> (10.69)
(TLR4-MD2) <sub>2</sub>	2	<b>-415.29</b> (72.99)	<b>-105.82</b> (7.04)	<b>450.54</b> (65.60)	<b>-16.07</b> (0.82)	<b>-86.63</b> (11.26)	<b>437.15</b> (67.02)	<b>-11.75</b> (0.58)	<b>-95.69</b> (12.47)
(TLR4-MD2) <sub>2</sub>	3	<b>-470.44</b> (52.58)	<b>-104.50</b> (6.58)	<b>492.72</b> (48.24)	<b>-16.83</b> (0.59)	<b>-99.03</b> (10.67)	<b>481.87</b> (47.50)	<b>-12.04</b> (0.40)	<b>-105.08</b> (11.19)
(TLR4-MD2) <sub>2</sub>	4	<b>-492.07</b> (66.78)	<b>-95.80</b> (6.99)	<b>517.40</b> (62.20)	<b>-15.27</b> (0.90)	<b>-85.73</b> (10.09)	<b>500.28</b> (61.22)	<b>-11.52</b> (0.63)	<b>-99.10</b> (12.00)
(TLR4-MD2) <sub>2</sub>	1-4	<b>-444.92</b> (43.23)	<b>-100.61</b> (5.29)	<b>473.45</b> (38.53)	<b>-15.74</b> (0.90)	<b>-87.80</b> (8.07)	<b>458.60</b> (39.29)	<b>-11.62</b> (0.36)	<b>-98.53</b> (4.82)
(TLR4-MD2-LPS) <sub>2</sub>	1	<b>-567.11</b> (48.40)	<b>-116.14</b> (7.22)	<b>592.14</b> (43.89)	<b>-18.54</b> (0.70)	<b>-109.63</b> (10.42)	<b>583.25</b> (44.25)	<b>-12.73</b> (0.42)	<b>-112.71</b> (11.60)
(TLR4-MD2-LPS) <sub>2</sub>	2	<b>-547.10</b> (53.04)	<b>-120.28</b> (7.77)	<b>580.17</b> (47.45)	<b>-18.72</b> (0.97)	<b>-105.92</b> (12.65)	<b>567.11</b> (46.63)	<b>-13.11</b> (0.74)	<b>-113.36</b> (15.97)
(TLR4-MD2-LPS) <sub>2</sub>	3	<b>-549.78</b> (63.52)	<b>-115.51</b> (8.24)	<b>584.28</b> (60.35)	<b>-17.82</b> (1.22)	<b>-98.81</b> (12.27)	<b>566.30</b> (62.55)	<b>-12.42</b> (0.79)	<b>-111.39</b> (14.22)
(TLR4-MD2-LPS) <sub>2</sub>	4	<b>-580.18</b> (70.14)	<b>-112.56</b> (7.65)	<b>599.07</b> (61.85)	<b>-18.14</b> (0.90)	<b>-111.80</b> (13.94)	<b>586.04</b> (59.56)	<b>-12.80</b> (0.48)	<b>-119.49</b> (17.09)
(TLR4-MD2-LPS) <sub>2</sub>	1-4	<b>-561.04</b> (15.54)	<b>-116.12</b> (3.18)	<b>588.92</b> (8.40)	<b>-18.31</b> (0.40)	<b>-106.54</b> (5.70)	<b>575.68</b> (10.43)	<b>-12.77</b> (0.28)	<b>-114.24</b> (3.60)
(TLR4-MD2-neoseptin3) <sub>2</sub>	1	<b>-483.32</b> (43.87)	<b>-106.69</b> (7.47)	<b>510.33</b> (40.04)	<b>-16.39</b> (0.93)	<b>-96.06</b> (11.58)	<b>491.43</b> (40.10)	<b>-11.62</b> (0.45)	<b>-110.19</b> (11.64)
(TLR4-MD2-neoseptin3) <sub>2</sub>	2	<b>-505.96</b> (55.91)	<b>-107.56</b> (7.17)	<b>530.87</b> (53.74)	<b>-16.52</b> (0.72)	<b>-99.15</b> (9.15)	<b>513.66</b> (52.82)	<b>-11.70</b> (0.51)	<b>-111.55</b> (11.48)
(TLR4-MD2-neoseptin3) <sub>2</sub>	3	<b>-588.88</b> (62.03)	<b>-109.72</b> (7.24)	<b>605.98</b> (58.38)	<b>-17.65</b> (0.87)	<b>-110.24</b> (9.82)	<b>589.74</b> (58.38)	<b>-12.53</b> (0.60)	<b>-121.37</b> (12.54)
(TLR4-MD2-neoseptin3) <sub>2</sub>	4	<b>-501.90</b> (50.60)	<b>-106.88</b> (7.35)	<b>524.92</b> (46.88)	<b>-16.70</b> (0.68)	<b>-100.54</b> (9.38)	<b>511.95</b> (46.12)	<b>-11.66</b> (0.36)	<b>-108.47</b> (11.21)
(TLR4-MD2-neoseptin3) <sub>2</sub>	1-4	<b>-520.02</b> (46.96)	<b>-107.71</b> (1.39)	<b>543.03</b> (42.85)	<b>-16.82</b> (0.57)	<b>-101.50</b> (6.12)	<b>526.70</b> (43.23)	<b>-11.88</b> (0.44)	<b>-112.90</b> (5.79)