

**Table S5.** 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)		$\Delta G$
		$\Delta E_{ele}$	$\Delta E_{vdw}$	$\Delta G_{sol}$		$\Delta G$	$\Delta G_{sol}$		
				$\Delta G_{pol}$	$\Delta G_{nonpol}$		$\Delta G_{pol}$	$\Delta G_{nonpol}$	
(TLR4-MD2) <sub>2</sub>	1	<b>4.47</b> (36.90)	<b>-38.74</b> (7.28)	<b>23.55</b> (33.15)	<b>-5.00</b> (0.96)	<b>-15.71</b> (6.82)	<b>12.09</b> (34.06)	<b>-4.81</b> (0.76)	<b>-26.97</b> (7.54)
(TLR4-MD2) <sub>2</sub>	2	<b>-60.50</b> (47.75)	<b>-55.51</b> (11.58)	<b>93.04</b> (45.30)	<b>-7.30</b> (1.68)	<b>-30.26</b> (11.76)	<b>83.81</b> (46.33)	<b>-6.79</b> (1.26)	<b>-38.97</b> (11.35)
(TLR4-MD2) <sub>2</sub>	3	<b>-50.35</b> (39.49)	<b>-33.67</b> (5.78)	<b>70.99</b> (37.36)	<b>-4.60</b> (0.76)	<b>-17.61</b> (6.11)	<b>57.80</b> (37.36)	<b>-4.34</b> (0.66)	<b>-30.54</b> (6.78)
(TLR4-MD2) <sub>2</sub>	4	<b>-33.03</b> (50.61)	<b>-33.99</b> (12.09)	<b>53.77</b> (51.33)	<b>-4.83</b> (1.89)	<b>-18.07</b> (9.88)	<b>46.29</b> (53.04)	<b>-4.39</b> (1.51)	<b>-25.11</b> (9.51)
(TLR4-MD2) <sub>2</sub>	1-4	<b>-34.85</b> (28.56)	<b>-40.48</b> (10.29)	<b>60.34</b> (29.32)	<b>-5.43</b> (1.26)	<b>-20.41</b> (6.64)	<b>50.00</b> (29.75)	<b>-5.08</b> (1.16)	<b>-30.40</b> (6.14)
(TLR4-MD2-LPS) <sub>2</sub>	1	<b>-120.80</b> (34.84)	<b>-78.00</b> (5.40)	<b>170.82</b> (33.87)	<b>-9.97</b> (0.90)	<b>-37.93</b> (6.26)	<b>167.08</b> (33.80)	<b>-8.02</b> (0.56)	<b>-39.71</b> (8.44)
(TLR4-MD2-LPS) <sub>2</sub>	2	<b>-142.00</b> (33.33)	<b>-73.00</b> (14.89)	<b>191.09</b> (35.17)	<b>-9.55</b> (2.01)	<b>-33.45</b> (9.91)	<b>190.02</b> (39.55)	<b>-7.70</b> (1.22)	<b>-32.67</b> (7.68)
(TLR4-MD2-LPS) <sub>2</sub>	3	<b>-264.03</b> (46.23)	<b>-72.56</b> (8.88)	<b>288.19</b> (44.52)	<b>-10.42</b> (1.13)	<b>-58.79</b> (9.13)	<b>278.58</b> (44.90)	<b>-8.27</b> (0.73)	<b>-66.25</b> (9.75)
(TLR4-MD2-LPS) <sub>2</sub>	4	<b>-142.75</b> (32.63)	<b>-72.84</b> (9.64)	<b>185.42</b> (28.66)	<b>-9.85</b> (1.35)	<b>-39.99</b> (11.06)	<b>176.64</b> (28.29)	<b>-7.96</b> (0.78)	<b>-46.87</b> (11.87)
(TLR4-MD2-LPS) <sub>2</sub>	1-4	<b>-167.40</b> (65.22)	<b>-74.10</b> (2.61)	<b>208.88</b> (53.56)	<b>-9.95</b> (0.36)	<b>-42.54</b> (11.17)	<b>203.08</b> (51.21)	<b>-7.99</b> (0.23)	<b>-46.38</b> (14.46)
(TLR4-MD2-neoseptin3) <sub>2</sub>	1	<b>-124.29</b> (48.80)	<b>-78.65</b> (10.16)	<b>171.30</b> (46.78)	<b>-9.92</b> (1.36)	<b>-41.55</b> (11.35)	<b>159.39</b> (47.20)	<b>-8.08</b> (0.79)	<b>-51.62</b> (12.99)
(TLR4-MD2-neoseptin3) <sub>2</sub>	2	<b>-200.25</b> (37.33)	<b>-76.45</b> (10.49)	<b>226.49</b> (32.29)	<b>-10.87</b> (1.21)	<b>-61.07</b> (9.63)	<b>220.36</b> (31.74)	<b>-8.18</b> (0.63)	<b>-64.51</b> (11.49)
(TLR4-MD2-neoseptin3) <sub>2</sub>	3	<b>-91.52</b> (31.26)	<b>-78.55</b> (9.09)	<b>136.69</b> (30.24)	<b>-9.77</b> (1.10)	<b>-43.13</b> (9.15)	<b>129.17</b> (30.78)	<b>-7.65</b> (0.64)	<b>-48.55</b> (9.88)
(TLR4-MD2-neoseptin3) <sub>2</sub>	4	<b>-65.26</b> (24.58)	<b>-69.29</b> (6.16)	<b>107.35</b> (23.79)	<b>-8.82</b> (0.80)	<b>-36.01</b> (5.73)	<b>101.86</b> (23.62)	<b>-7.06</b> (0.44)	<b>-39.73</b> (6.59)
(TLR4-MD2-neoseptin3) <sub>2</sub>	1-4	<b>-120.33</b> (58.50)	<b>-75.74</b> (4.41)	<b>160.46</b> (51.20)	<b>-9.85</b> (0.84)	<b>-45.44</b> (10.86)	<b>152.70</b> (50.86)	<b>-7.74</b> (0.51)	<b>-51.10</b> (10.26)