



**Supplementary Figure 1.** (A) S5.43(O $\gamma$ )-Water(O) and (B) N6.55(N $\delta$ )-Water(O) radial distribution functions for compounds **1** (solid line) and **3** (dashed line) in the receptor-lipid systems. Clearly, S5.43 is mostly buried from bulk water while N6.55 is partially solvated. The binding of the 6-choro derivative **3** (dashed line) to N6.55 allows a single water molecule to hydrogen bond S5.43 (shown by the small peak at 2 Å). In addition, the first solvation shell around N6.55 is more closely packed for unsubstituted derivative **1** (solid line) than the 6-choro derivative **3** (dashed line) as shown by the larger area at ~4.8 Å.