SUPPORTING MATERIAL:
A METHOD TO PREDICT BLOOD-BRAIN BARRIER PERMEABILITY OF DRUG-LIKE COMPOUNDS USING MOLECULAR DYNAMICS SIMULATIONS

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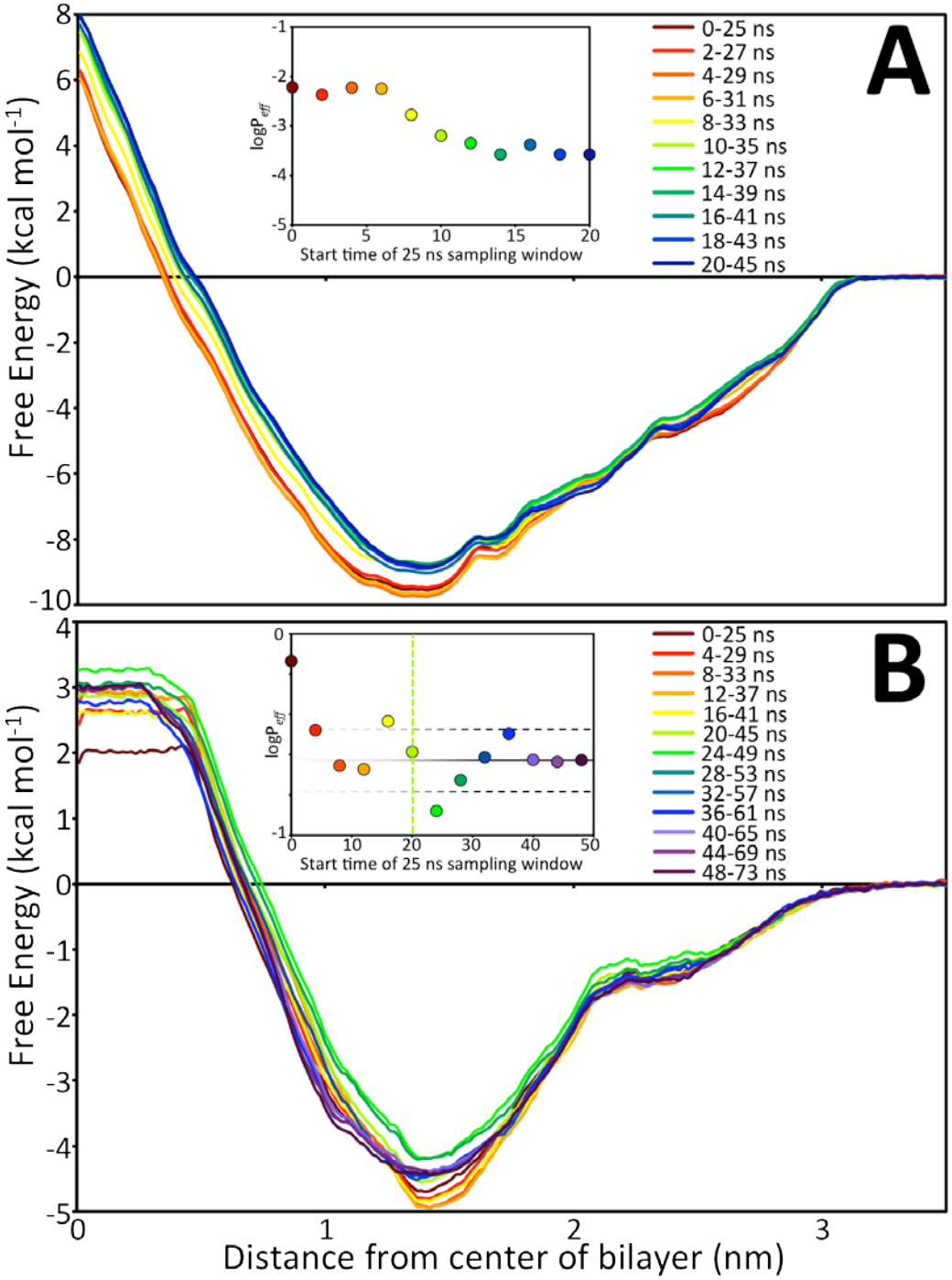

Figure S1. In order to check the equilibration and convergence of the umbrella sampling simulation windows, 25 ns 'slices' were taken through the trajectory and used to calculate the PMF and subsequent $logP_{eff}$ of the specific compound. These curves and values are colored according to time. Most PMF curves and $logP_{eff}$ values converged well within the 20 ns equilibration used as standard within our protocol, such as the charged species of atenolol (**A**). However, some species, such as the neutral form of salicylate (**B**), did not reach a converged value within the first 20 ns. In these cases, extended simulations (sometimes including an increased resolution in umbrella sampling windows) were needed. For salicylate, it appears to take ~30 ns to converge to values that fall within the same error range (black dashed lines – measured using bootstrapping error calculations).

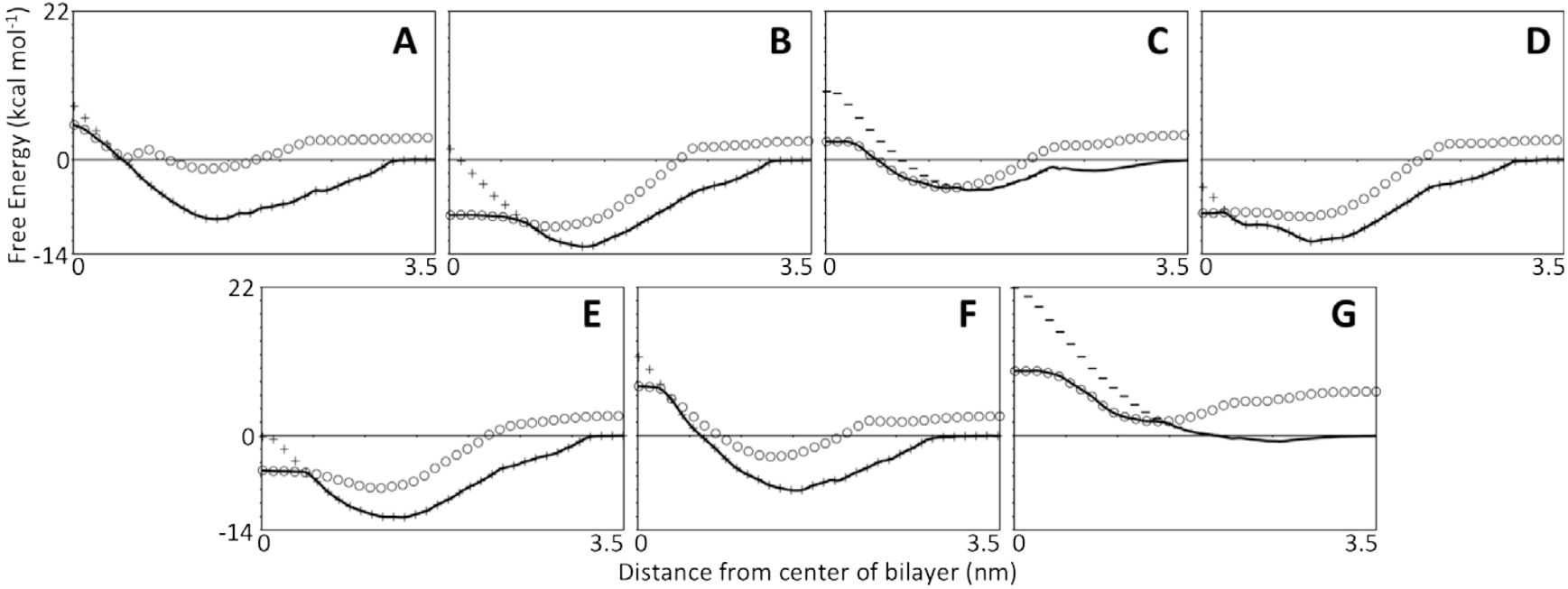

Figure S2. The individual PMFs for the neutral (indicated by 'o') and charged species (indicated by '+' or '-') of atenolol (**A**), chlorpromazine (**B**), ibuprofen (**C**), imipramine (**D**), promazine (**E**), salbutamol (**F**) , and salicylate (**G**). The solid black line follows the lowest PMF value at each point. These compounds exist primarily in a charged state at physiological pH. As such, PMFs curves were calculated for both their charged and neutral species. The neutral PMFs have been offset by the free energy required to neutralize the compound in bulk water at pH 7.4, according to each compound's experimentally measured pKa, and the methodology used by MacCallum *et al*. [1].

References

1. MacCallum, J.L., W.F.D. Bennett, and D.P. Tieleman, *Distribution of amino acids in a lipid bilayer from computer simulations.* Biophysical Journal, 2008. **94**(9): p. 3393-3404.