Electronic Supplementary Material (ESI) for Physical Chemistry Chemical Physics.

SUPPORTING INFORMATION

DO DRUGS ADSORBED TO P-GLYCOPROTEIN INFLUENCE ITS EFFLUX CAPABILITY?

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Table S1. Distribution of molecules between the two interfaces (and bulk water) for all considered classes (mean values ± standart deviation).

Figure S1. Root mean square deviation (RMSD) for the protein (after 150 ns).

Figure S2. Free energies of adsorption ($kJ.mol^{-1}$) to the protein and lipid bilayer for each molecule.

Figure S3. MM/PBSA interaction energies for each molecule.

Figures S4-S6. Hydrogen bonding results for each molecule.

Figures S7-S18. Membrane-deformation profiles *u(x,y)* for P-glycoprotein in the presence of each molecule.

Figures S19-S30. Variation of the residual exposure energy penalty ($\Delta\Delta G_{res}$) for each molecule, compared with the *apo* system.

Figures S31-S33. Area per lipid as a function of time for the *apo* system and several molecules.

Table S1. Distribution of molecules between the two interfaces (and bulk water) for all considered classes (mean values ± standart deviation).

Molecule	Protein-Water Interface	Lipid-Water Interface	Not adsorbed (bulk water)
ATP	5±2	4±2	1
Non-substrates	3±2	6±1	7±1
Substrates	7±2	5±1	3±2
Modulators	6±1	4±1	4±1

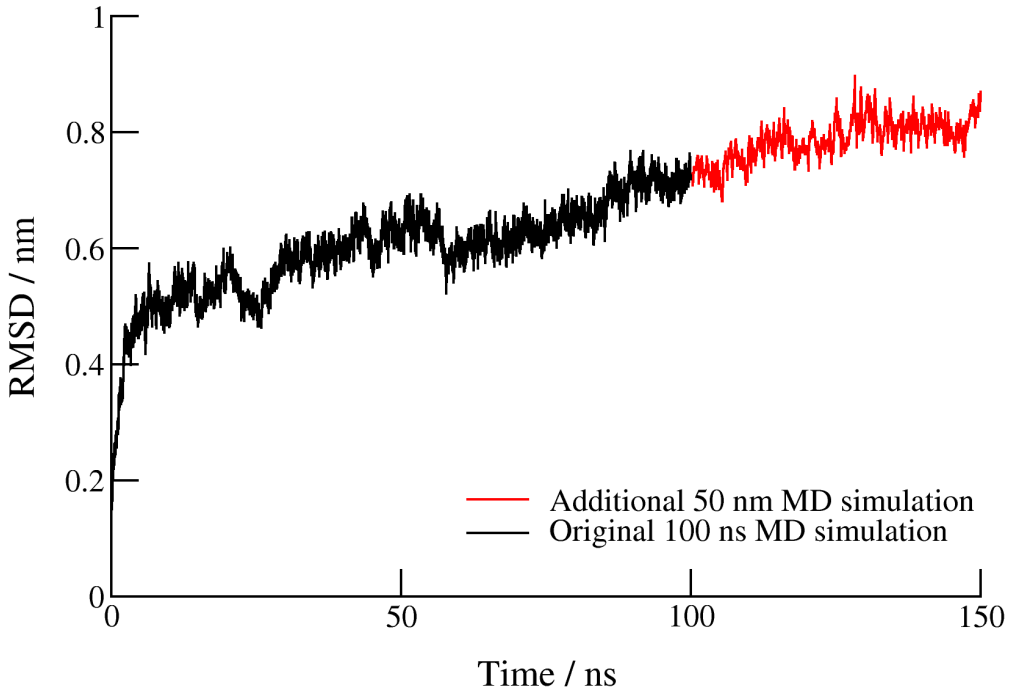


Figure S1. Root mean square deviation (RMSD) for the protein (after 150 ns). See also Chart 4 in Ref. 25 and discussion that follows.

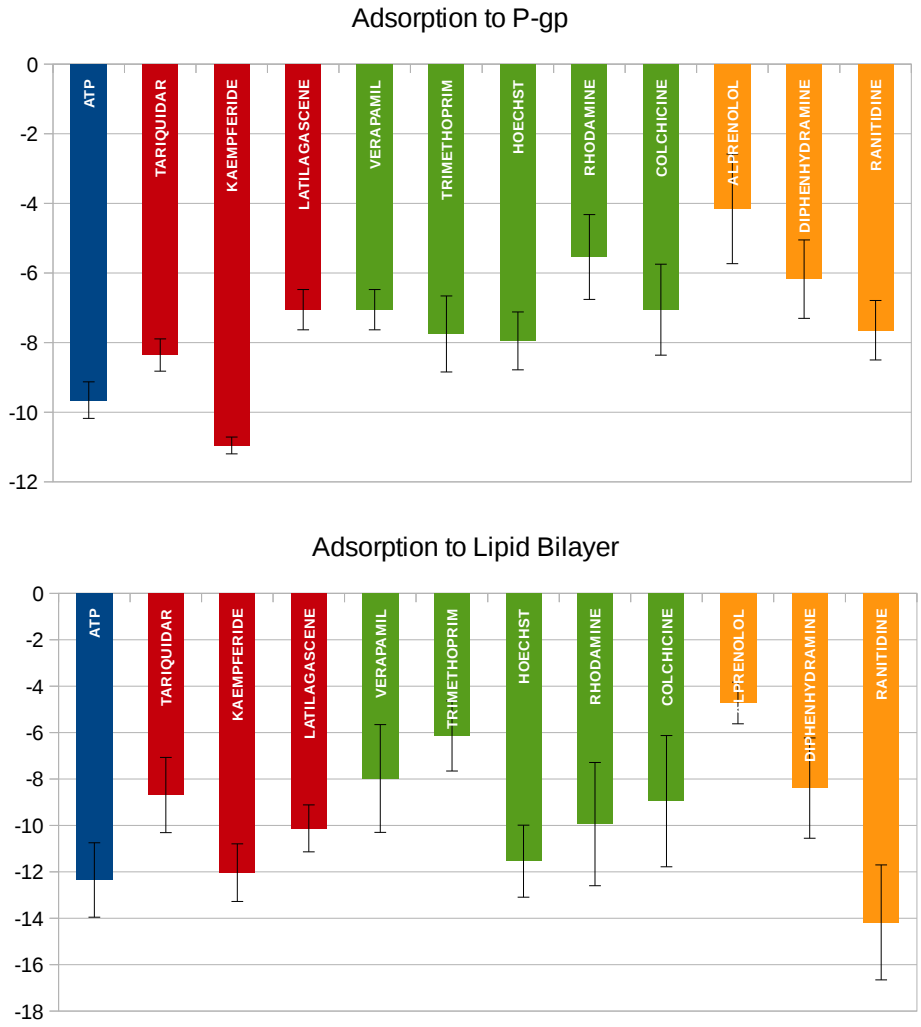


Figure S2. Calculated free energies of adsorption (ΔG_{ads}, kJ.mol^{-1}) to the protein-water (top) and lipid-water (bottom) interfaces.

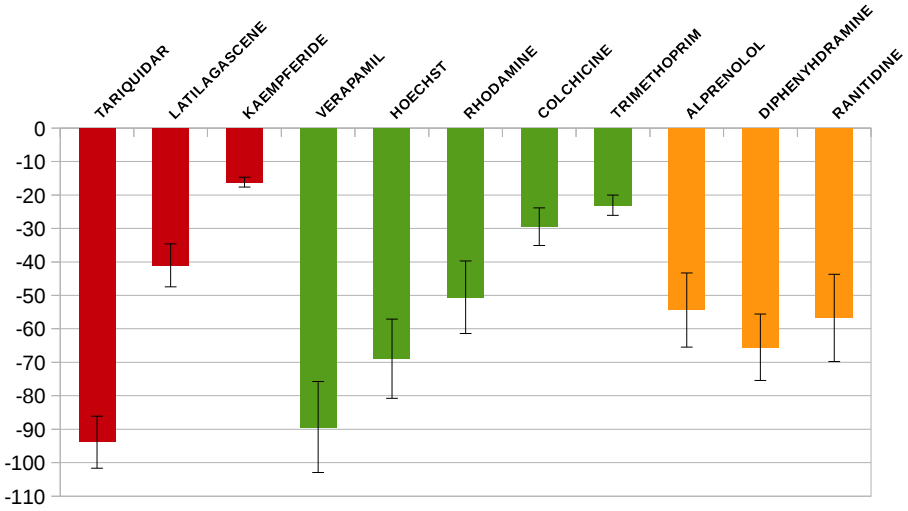


Figure S3. MM/PBSA relative interaction free energies (kJ.mol^{-1}) for each molecule (as calculated with *g_mmpbsa* with the implicit membrane correction for polar solvation energies).

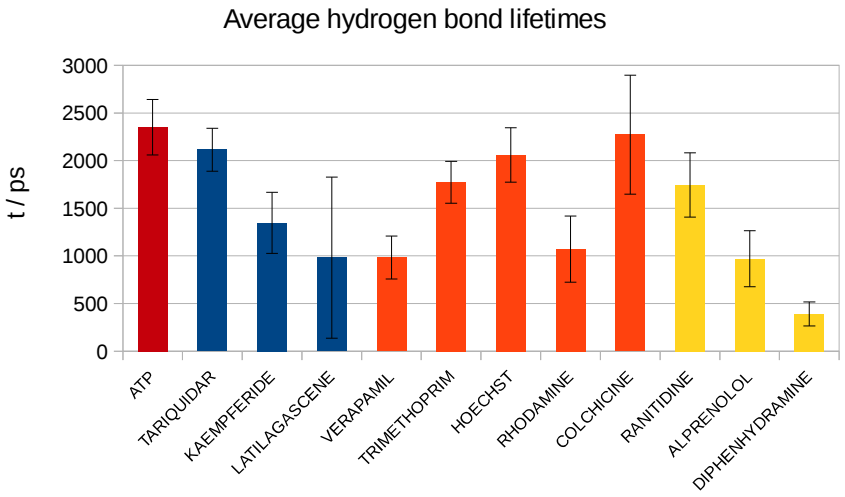


Figure S4. Average hydrogen bond lifetimes (mean ± SE) for each molecule.

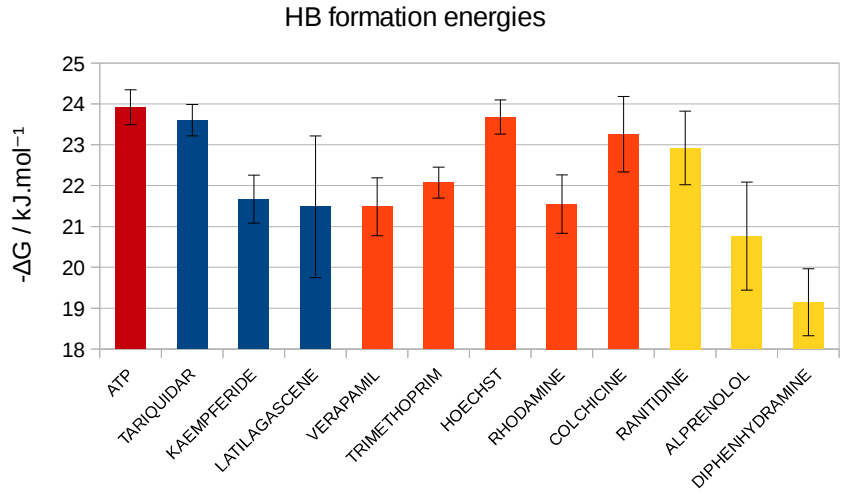


Figure S5. Hydrogen bond formation energies (mean ± SE) for each molecule.

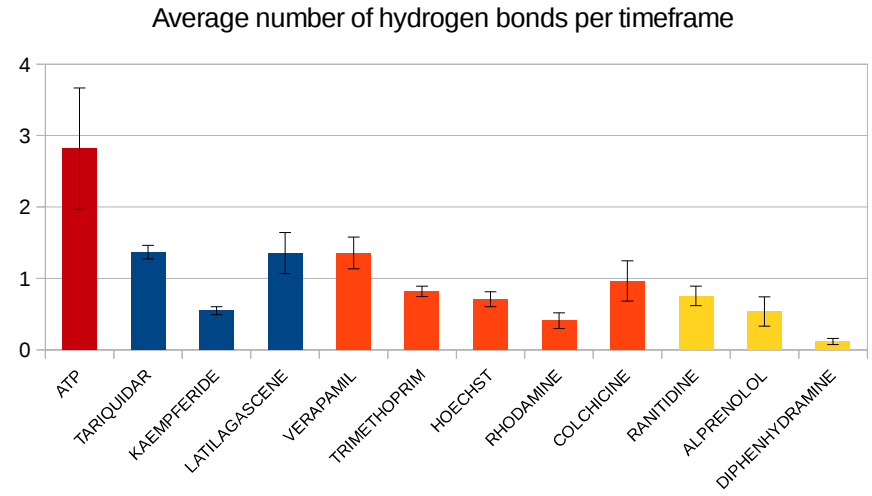
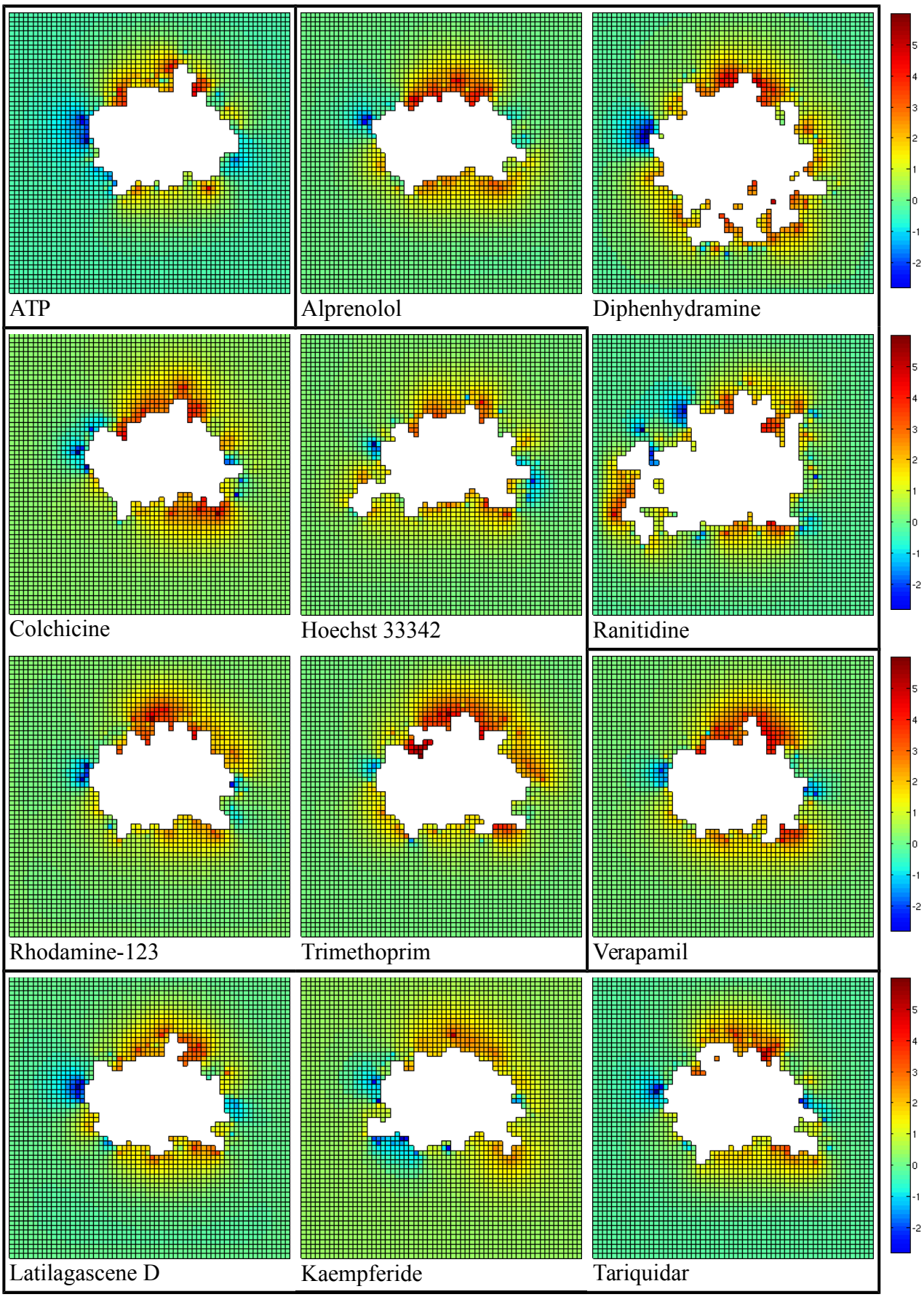
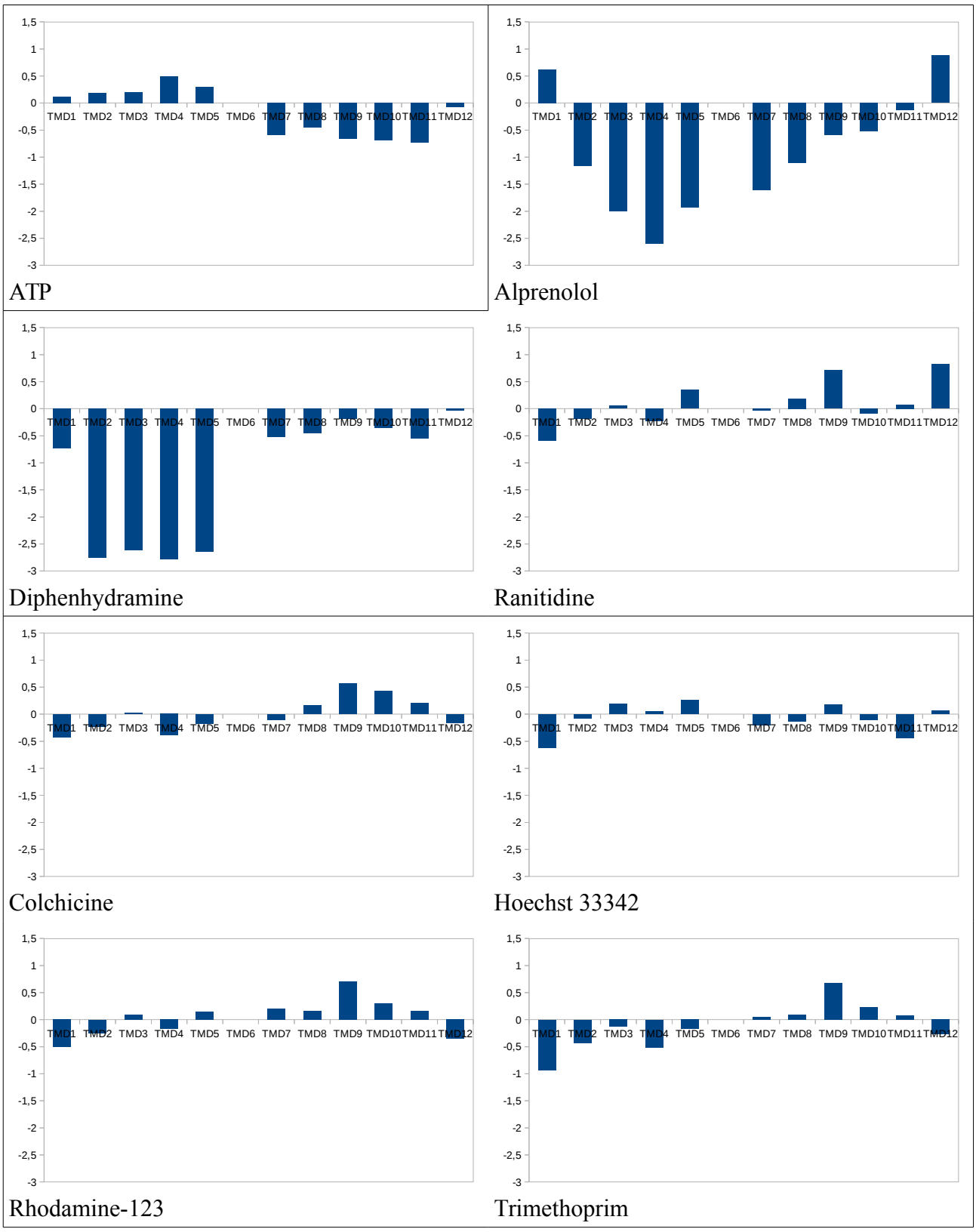


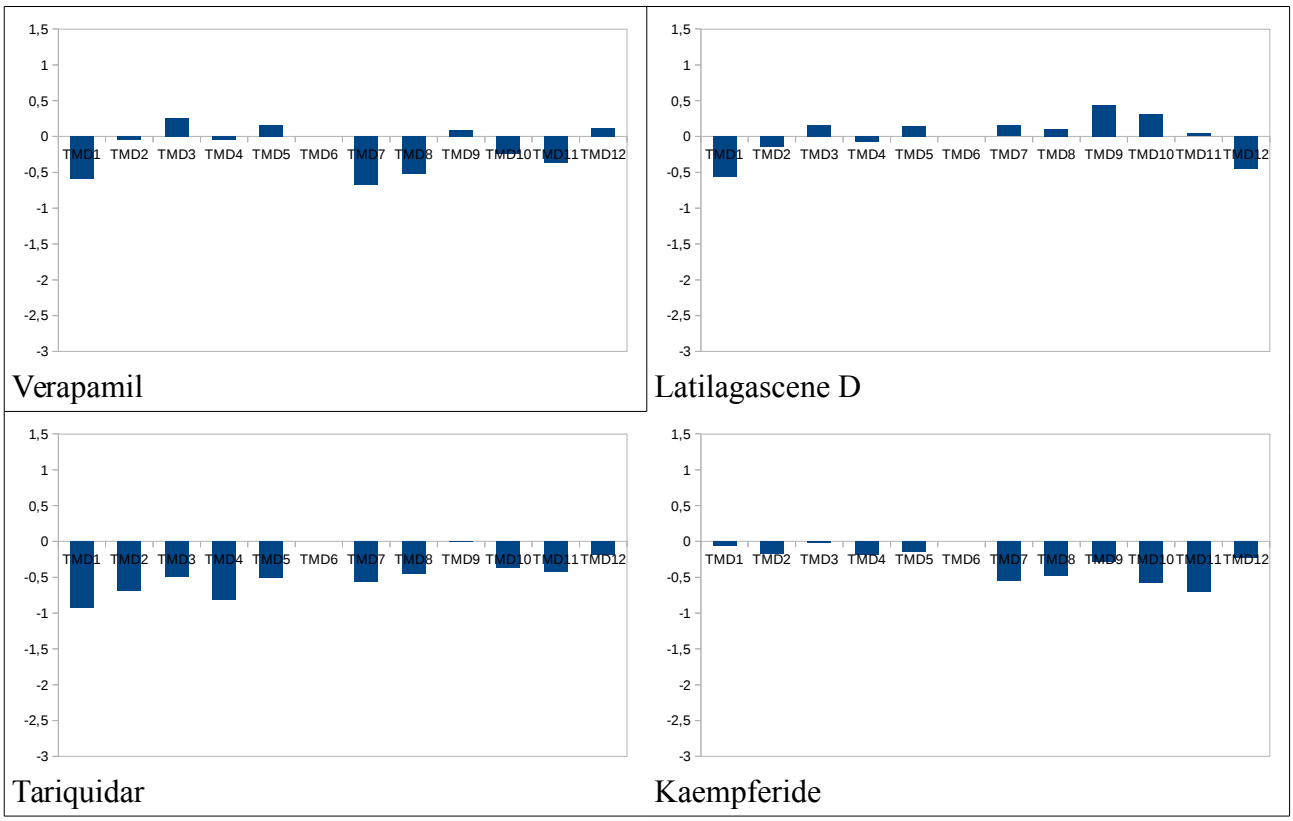
Figure S6. Average number of hydrogen bonds per timeframe (mean ± SE) for each molecule.



Figures S7-S18. Membrane-deformation profiles *u(x,y)* for P-glycoprotein in the presence of each molecule (units in k_BT).



Figures S19-26. Variation of the residual exposure energy penalty ($\Delta\Delta G_{res}$, kJ.mol^{-1}) for each molecule, compared with the *apo* system.



Figures S27-30. Variation of the residual exposure energy penalty ($\Delta\Delta G_{res}$, kJ.mol^{-1}) for each molecule, compared with the *apo* system.

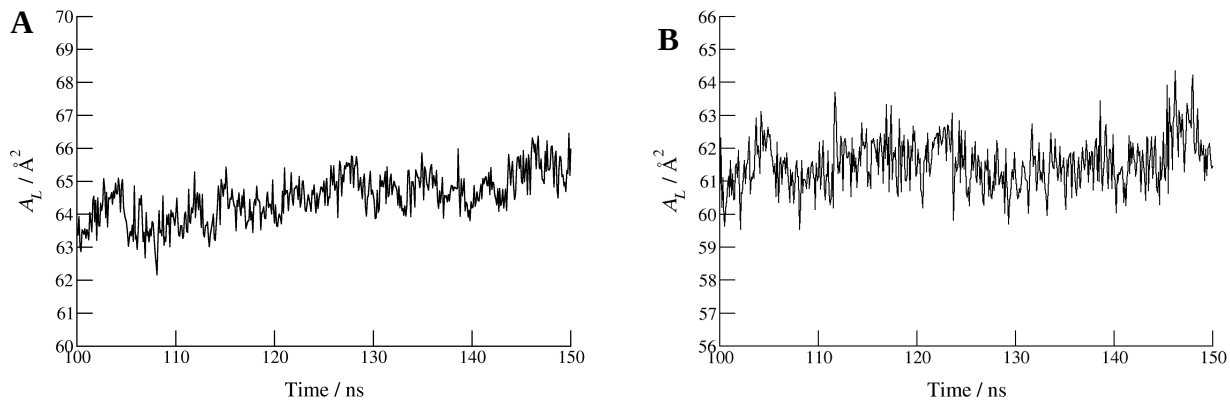


Figure S31. Area per lipid (A_L) as a function of time for the *apo* system. (A), upper leaflet; (B), lower leaflet.

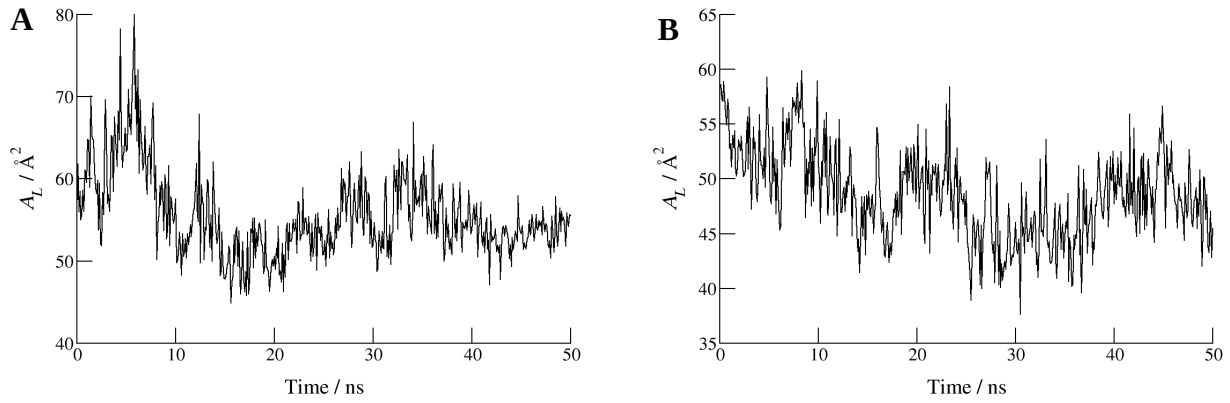


Figure S32. Area per lipid (A_L) of the lower leaflet as a function of time for *substrates* Hoechst 33342 (A) and Rhodamine-123 (B).

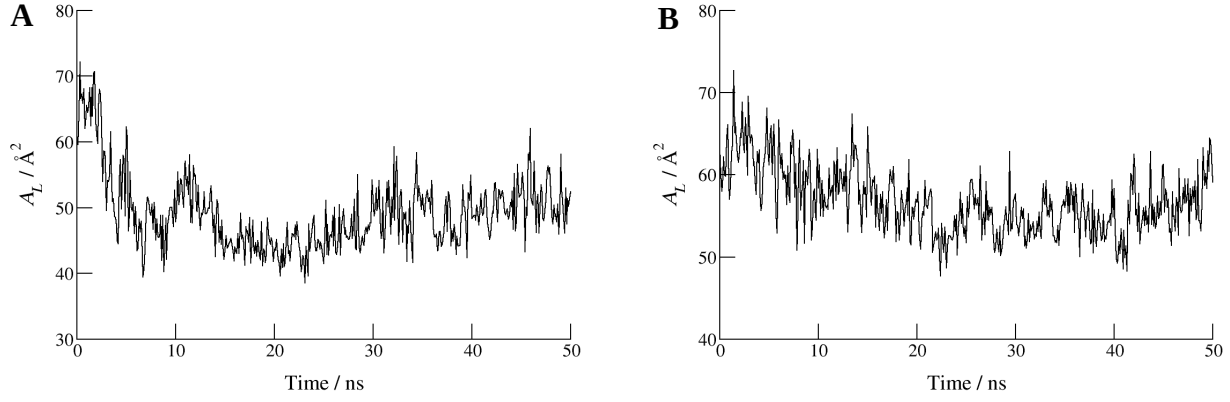


Figure S33. Area per lipid (A_L) of the lower leaflet as a function of time for *modulators* tariquidar (A) and kaempferide (B).