SUPPLEMENTARY INFORMATION

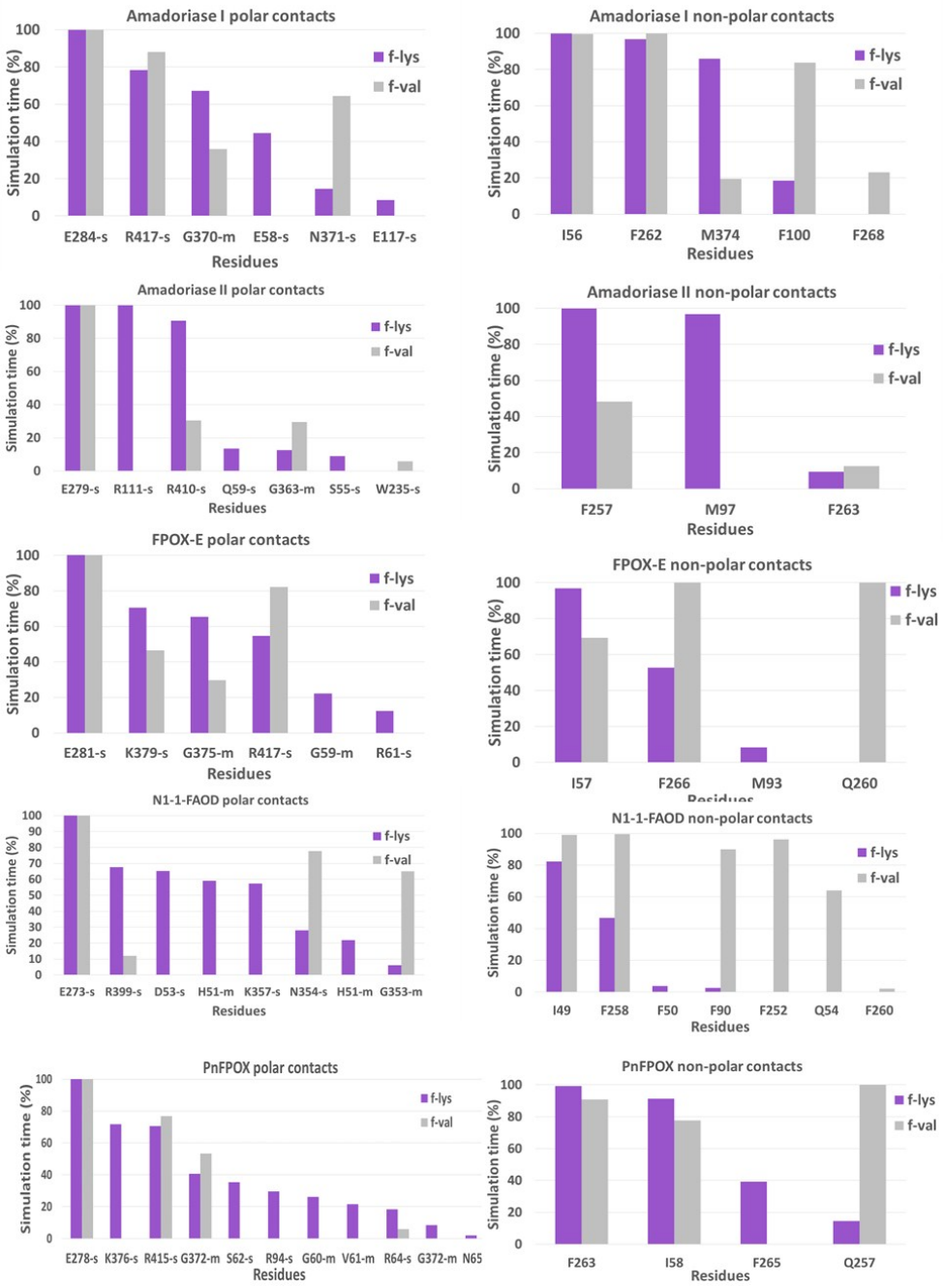
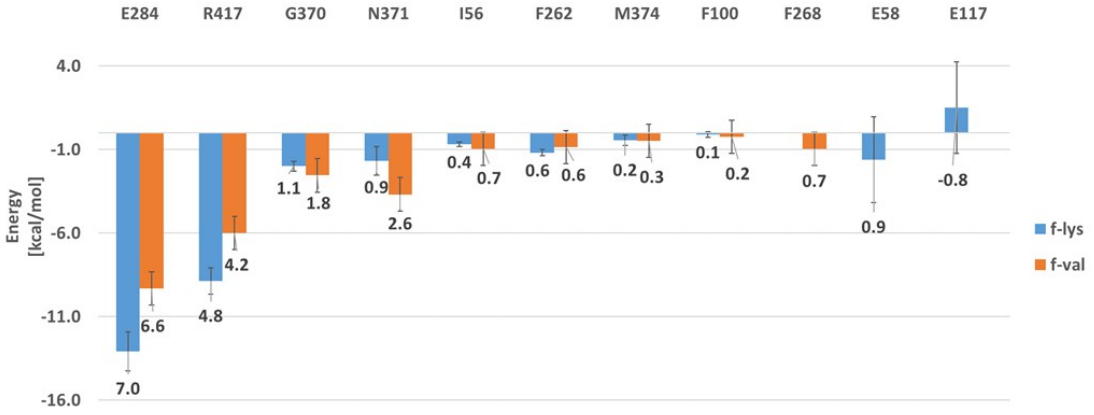
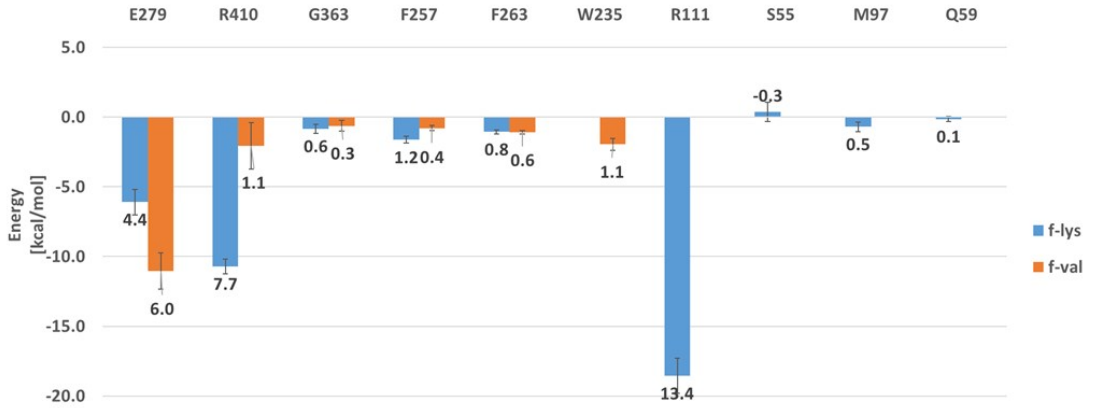


Figure S1. Lists of polar and nonpolar interactions of each enzyme with both ligands. A threshold of 2 % of persistence during simulation time is applied to select interactions for analysis. The durability of the contacts is evaluated along the MD trajectory by analyzing the frames where the ligand-sugar moiety is stable and correctly positioned in the catalytic pocket. Therefore, the percentage reported in the table are relative to the time of complex stability.

Amadoriase I



Amadoriase II



FPOX-E

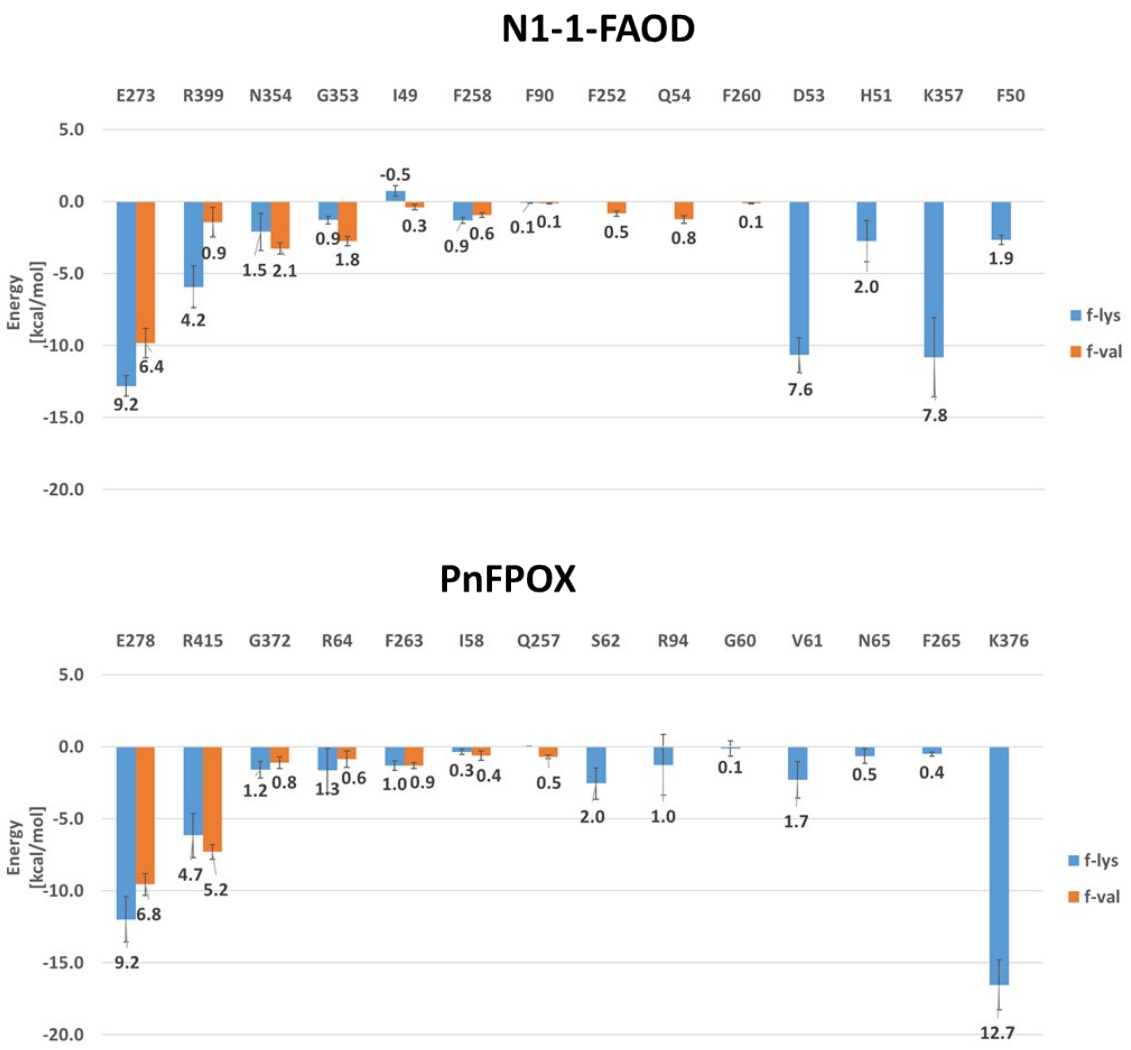


Figure S2. Decomposition of the enthalpic component of the binding free energy contribution on the enzyme residues that mostly interact with the ligands. The labels at the top of each histogram are the percentage of relative contribution compared to the total enzyme-ligand interactions.

Enzyme	f-lys		f-val	
	PSASAD	ε_{int}	PSASAD	ε_{int}
Amadoriase I	71	4	27	2
Amadoriase II	43	3	30	2
FPOX-E	61	3	47	3
N1-1-FAOD	51	3	34	2
PnFPOX	52	3	33	2

Table S1. The PSASAD is defined as the Solvent Accessible Surface Area Difference (SASAD) between ligand-bonded and apo states of the protein polar atoms that strongly interact with the ligand. To calculate PSASAD, we chose polar atoms within a 5 Å distance from f-lys or f-val for each enzyme and we estimated SASAD with and without ligands. We excluded the f-val hydrophobic tail from the SASA calculation owing to its inability to interact with polar atoms. Due to the charged nature of the binding interface for all the enzymes, we limited our choice of internal dielectric constant (ε_{int}) to values greater than 2. Based on the PSASAD calculation, all enzymes show a ε_{int} in the range between 2.0 and 4.0. For binding energy calculations, we restricted our analysis to those frames where the sugar moiety of the ligand is correctly positioned within the catalytic pocket. The binding energy was then computed as the average over all the relevant frames of the trajectory.