Table S1: Experimental binding free energies $\Delta G_{\text{exp}}$ (kJ mol$^{-1}$) as derived from inhibition data reported by Vaz et al. [9] for individual training compounds (numbered here according to the compound indices used by Vaz et al.). In addition, calculated values $\Delta G_{\text{calc}}$ (kJ mol$^{-1}$) are reported using either $\langle V_{\text{rel}}^{\text{lig-surr}} \rangle$’s and $\langle V_{\text{vdW}}^{\text{lig-surr}} \rangle$’s in Equation (3) averaged over full production runs (ns) or over time spans selected according to the protocol described in the Methods section with $L = 200$ ps, together with their corresponding difference from experiment ($\Delta \Delta G = \Delta G_{\text{exp}} - \Delta G_{\text{calc}}$). RMSE (kJ mol$^{-1}$), $\alpha$ and $\beta$ values are also reported for the filtered LIE models (with $L$ set to 200 ps) in which the corresponding single training compound was left out from model training.

| Compound | $\Delta G_{\text{exp}}$ (ns) | $\Delta G_{\text{calc}}$ (ns) | $\Delta G_{\text{calc}}$ (filt.) | $\Delta \Delta G$ (filt.) | RMSE | $\alpha$ | $\beta$ |
|----------|-----------------|-----------------|-----------------|-----------------|------|--------|--------|
| 1        | -31.7           | -32.9           | 1.1             | -33.3           | 1.6  | 5.84   | 0.442  | 0.089 |
| 2        | -28.4           | -38.5           | 10.2            | -37.2           | 8.8  | 5.65   | 0.443  | 0.092 |
| 3        | -31.3           | -34.4           | 3.0             | -35.9           | 4.6  | 5.79   | 0.442  | 0.094 |
| 4        | -35.7           | -31.4           | -4.3            | -31.5           | -4.2 | 5.79   | 0.441  | 0.085 |
| 5        | -48.2           | -41.6           | -6.6            | -42.1           | -6.1 | 5.74   | 0.439  | 0.088 |
| 6        | -31.7           | -26.8           | -5.0            | -26.9           | -4.9 | 5.77   | 0.441  | 0.083 |
| 7        | -37.5           | -32.0           | -5.6            | -30.3           | -7.3 | 5.70   | 0.440  | 0.085 |
| 8        | -27.3           | -34.4           | 7.0             | -35.1           | 7.8  | 5.67   | 0.444  | 0.086 |
| 9        | -31.0           | -34.2           | 3.2             | -34.7           | 3.7  | 5.81   | 0.442  | 0.087 |
| 10       | -30.6           | -24.2           | -6.4            | -23.9           | -6.7 | 5.71   | 0.441  | 0.082 |
| 11       | -33.0           | -34.0           | 1.0             | -35.4           | 2.4  | 5.83   | 0.442  | 0.088 |
| 12       | -41.4           | -49.4           | 8.0             | -46.6           | 5.1  | 5.77   | 0.443  | 0.086 |
| 13       | -46.9           | -42.1           | -4.8            | -43.7           | -3.2 | 5.82   | 0.440  | 0.088 |
| 14       | -48.2           | -34.1           | -14.2           | -34.5           | -13.8| 5.32   | 0.438  | 0.088 |
| 15       | -33.7           | -34.5           | 0.8             | -33.2           | -0.5 | 5.84   | 0.441  | 0.088 |
| 16       | -45.7           | -53.4           | 7.7             | -56.3           | 10.6 | 5.53   | 0.446  | 0.090 |
| 17       | -46.9           | -40.1           | -6.8            | -38.9           | -8.0 | 5.66   | 0.439  | 0.085 |
| 18       | -42.2           | -44.6           | 2.4             | -44.3           | 2.0  | 5.83   | 0.442  | 0.089 |
| 21       | -46.9           | -46.4           | 0.5             | -46.4           | -0.5 | 5.84   | 0.441  | 0.088 |
| 22       | -42.5           | -43.5           | 1.0             | -42.1           | -0.4 | 5.84   | 0.441  | 0.087 |
| 23       | -44.6           | -39.5           | -5.2            | -46.4           | 1.7  | 5.83   | 0.442  | 0.086 |
| 24       | -46.9           | -40.1           | -6.8            | -40.4           | -6.5 | 5.73   | 0.439  | 0.088 |
| 25       | -35.1           | -32.1           | -3.0            | -34.5           | -0.6 | 5.84   | 0.441  | 0.088 |
| 26       | -46.9           | -37.5           | -9.4            | -37.6           | -9.3 | 5.61   | 0.439  | 0.089 |
| 27       | -47.5           | -54.2           | 6.7             | -50.8           | 3.3  | 5.81   | 0.443  | 0.087 |
| 28       | -41.9           | -38.7           | -3.2            | -38.5           | -3.4 | 5.83   | 0.440  | 0.094 |
| 29       | -46.0           | -48.2           | 2.1             | -48.7           | 2.7  | 5.82   | 0.442  | 0.087 |
| 30       | -47.5           | -56.3           | 8.9             | -54.3           | 6.9  | 5.70   | 0.445  | 0.083 |
| 31       | -44.9           | -52.7           | 7.8             | -49.0           | 4.1  | 5.80   | 0.443  | 0.089 |
| 32       | -45.4           | -38.4           | -7.0            | -37.9           | -7.5 | 5.68   | 0.440  | 0.084 |
| 33       | -44.6           | -40.5           | -4.1            | -41.7           | -2.9 | 5.83   | 0.440  | 0.090 |
| 34       | -48.2           | -45.4           | -2.8            | -46.1           | -2.2 | 5.83   | 0.441  | 0.087 |
| 35       | -47.5           | -44.5           | -3.0            | -44.9           | -2.6 | 5.83   | 0.441  | 0.088 |
| 36       | -40.2           | -47.1           | 6.9             | -47.9           | 7.7  | 5.69   | 0.444  | 0.096 |