Supplementary file

**Supplementary Table 1.** The basic parameters of equilibration steps.

| Stage of equilibration | Ensemble | Integration step, fs | Simulation time, ps | Force of non-H atoms position restraints, kJ/mol/nm² |
|-------------------------|----------|----------------------|--------------------|---------------------------------------------------|
|                         |          |                      |                    | Main chain | Side chain | Lligand | Lipid head |
| 1                       | NVT      | 1                    | 25                 | 4000       | 2000       | 4000    | 1000       |
| 2                       | NVT      | 1                    | 25                 | 2000       | 1000       | 2000    | 1000       |
| 3                       | NPT      | 1                    | 25                 | 1000       | 500        | 1000    | 400        |
| 4                       | NPT      | 2                    | 100                | 500        | 200        | 500     | 200        |
| 5                       | NPT      | 2                    | 100                | 200        | 50         | 200     | 40         |
| 6                       | NPT      | 2                    | 100                | 50         | 0          | 50      | 0          |

**Supplementary Figure 1.** Mass spectrometry on the Bruker UltraFlex II MALDI-TOF time-of-flight mass spectrometer with flexControl 1.1 and flexAnalys 2.2 software for mass spectra acquisition and processing.

H-His-Rim, matrix IAA (3β-indolacrylic acid)
Supplementary Figure 2. Spectral data for the compound HCl*H-His-Rim

NMR C\textsuperscript{13}

NMR H\textsuperscript{1}
**Supplementary Table 2.** Linear interaction energy by trajectory slicing.

| Protein | Ligand conf. | $t_{\text{start}}$, ns. | $t_{\text{end}}$, ns. | $<\text{LIE}>$, kJ/mol | $\sigma$(LIE), kJ/mol | $\text{LIE}_{\text{min}}$, kJ/mol | $\text{LIE}_{\text{max}}$, kJ/mol |
|---------|--------------|-------------------------|------------------------|-------------------------|-----------------------|-----------------------------------|-----------------------------------|
| S31N    | Deep         | 0                       | 20                     | 13.1                    | 18.4                  | -69.0                             | 95.4                              |
|         | Middle       | 0                       | 20                     | 54.5                    | 21.6                  | -13.3                             | 168.3                             |
|         | Middle       | 0                       | 1.75                   | 102.7                   | 16.6                  | 49.5                              | 168.3                             |
|         | Middle       | 1.8                     | 20                     | 49.8                    | 15.5                  | -13.3                             | 112.6                             |
|         | Surface      | 0                       | 20                     | -15.2                   | 21.9                  | -106.3                            | 65.0                              |
| S31N_A30T | Surface    | 0                       | 20                     | -30.0                   | 22.2                  | -112.1                            | 58.9                              |
|         | Deep         | 0                       | 20                     | 45.7                    | 12.31                 | -9.8                              | 99.6                              |
|         | Middle       | 0                       | 20                     | 39.2                    | 34.1                  | -71.6                             | 148.1                             |
|         | Middle       | 0                       | 10.275                 | 65.8                    | 23.5                  | 5.4                               | 148.1                             |
|         | Middle       | 10.325                  | 20                     | 11.0                    | 16.6                  | -71.6                             | 75.7                              |