Supplementary material for the article:

Molecular Dynamics Simulation and Linear Interaction Energy Study of D-Glu-Based Inhibitors of the MurD Ligase

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**Keywords** Molecular dynamics (MD) simulations, Linear interaction energy (LIE) method, structure-based pharmacophore models, MurD ligase, antibacterial agents, drug design

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1. Structural alignment of 2XPC, 2X68, 2X50 and 2JFF crystal structures

**Fig 1S.** Structural alignment of 2XPC (silver), 2X68 (yellow), 2X50 (orange), 2JFF (red) MurD crystal structures. The positions of the bound inhibitors - compounds 1-4 - are indicated.
2. Outline of the LIE study of D-Glu-based MurD Ligase inhibitors

**Fig 3S.** Outline of the steps in the performed Linear Interaction energy (LIE) study of the D-Glu-based MurD Ligase inhibitors.
3. Schematic representation of the thermodynamic cycle applied in the LIE method

Fig 2S. Thermodynamic cycle applied in LIE method. \( L \) represents the ligand, \( P \) represents the protein. Blue circle \( W \) symbolizes water. Dashed line surrounding the ligand denotes decoupling – switching off the non-bonding (electrostatic and non-polar) interactions.
4. RESP partial charges and atoms types for simulated Compounds 2-4

Table S1. Atom types and partial RESP atomic charges for Compound 2.

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Table S2. Atom types and partial RESP atomic charges for Compound 3.

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5. Decomposition schemes for simulated Compounds 2-4

Compound 1*

Compound 2

Compound 3

Compound 4

*data previously published in ref 15
6. Average distances of compounds 2-4 for each independent MD simulation

Table 4S.1. Average distances between compound 2 and selected MurD residues for the D-Glu based interactions: (a) side chain oxygen of Thr321 and α-carboxylic oxygen of 2 (b) side chain nitrogen of Lys348 and α-carboxylic oxygen of 3 (c) backbone nitrogen of Ser415 and γ-carboxylic oxygen of 3 (d) side chain oxygen of Ser415 and γ-carboxylic oxygen of 2 (e) backbone nitrogen of Phe422 and γ-carboxylic oxygen of 2.

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<th>Thr321 [Å]</th>
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<th>Ser415 (N) [Å]</th>
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Table 4S.2. Average distances between compound 3 and selected MurD residues for the D-Glu based interactions: (a) side chain oxygen of Thr321 and α-carboxylic oxygen of 3 (b) side chain nitrogen of Lys348 and α-carboxylic oxygen of 3 (c) backbone nitrogen of Ser415 and γ-carboxylic oxygen of 3 (d) side chain oxygen of Ser415 and γ-carboxylic oxygen of 3 (e) backbone nitrogen of Phe422 and γ-carboxylic oxygen of 3.

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Table 4S.3. Average distances between compound 4 and selected MurD residues for the D-Glu based interactions: (a) side chain oxygen of Thr321 and first carboxylic oxygen of 4 (b) side chain nitrogen of Lys348 and first carboxylic oxygen of 4 (c) backbone nitrogen of Ser415 and second carboxylic oxygen of 4 (d) side chain oxygen of Ser415 and second carboxylic oxygen of 4 (e) backbone nitrogen of Phe422 and second carboxylic oxygen of 4.

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<th>Thr321 [Å]</th>
<th>Lys348 [Å]</th>
<th>Ser415 (N) [Å]</th>
<th>Ser415 (O) [Å]</th>
<th>Phe422 [Å]</th>
</tr>
</thead>
<tbody>
<tr>
<td>4_1</td>
<td>3.84</td>
<td>2.90</td>
<td>3.02</td>
<td>2.71</td>
<td>3.21</td>
</tr>
<tr>
<td>4_2</td>
<td>3.56</td>
<td>2.75</td>
<td>3.22</td>
<td>3.04</td>
<td>3.90</td>
</tr>
<tr>
<td>4_3</td>
<td>3.46</td>
<td>3.21</td>
<td>3.45</td>
<td>3.08</td>
<td>4.07</td>
</tr>
<tr>
<td>4_4</td>
<td>3.80</td>
<td>2.77</td>
<td>3.50</td>
<td>3.19</td>
<td>3.44</td>
</tr>
</tbody>
</table>

Table 5S.1. Average distances between compound 2 and selected MurD residues for the following monitored H-bond interactions: (a) ND1 nitrogen of His183 and amide oxygen of 3 (b) NE2 nitrogen of His183 and oxygen of the amide moiety of 2 (c) backbone nitrogen of Thr36 and interacting moiety of compounds 2 (i) side chain oxygen of Thr36 and interacting moiety of compounds 2.

<table>
<thead>
<tr>
<th>Compound</th>
<th>His183 (1) [Å]</th>
<th>His183 (2) [Å]</th>
<th>Thr36 (N) [Å]</th>
<th>Thr36 (O) [Å]</th>
</tr>
</thead>
<tbody>
<tr>
<td>2_1</td>
<td>3.59</td>
<td>4.42</td>
<td>3.44</td>
<td>5.74</td>
</tr>
<tr>
<td>2_2</td>
<td>3.85</td>
<td>4.23</td>
<td>3.44</td>
<td>5.83</td>
</tr>
<tr>
<td>2_3</td>
<td>3.54</td>
<td>4.41</td>
<td>3.40</td>
<td>5.77</td>
</tr>
<tr>
<td>2_4</td>
<td>3.62</td>
<td>4.33</td>
<td>3.43</td>
<td>5.77</td>
</tr>
</tbody>
</table>
Table 5S.2. Average distances between compounds 3 and selected MurD residues for the following monitored H-bond interactions: (a) ND1 nitrogen of His183 and oxygen of 3 sulfonamide moiety (b) NE2 nitrogen of His183 and oxygen of 1-4 sulfonamide moiety (c) backbone nitrogen of Thr36 and interacting moiety of compound 3 (i) side chain oxygen of Thr36 and interacting moiety of compound 3.

<table>
<thead>
<tr>
<th>Compound</th>
<th>His183 (1) [Å]</th>
<th>His183 (2) [Å]</th>
<th>Thr36 (N) [Å]</th>
<th>Thr36 (O)[Å]</th>
</tr>
</thead>
<tbody>
<tr>
<td>3_1</td>
<td>3.65</td>
<td>4.39</td>
<td>3.64</td>
<td>5.75</td>
</tr>
<tr>
<td>3_2</td>
<td>3.97</td>
<td>5.11</td>
<td>3.64</td>
<td>5.83</td>
</tr>
<tr>
<td>3_3</td>
<td>4.13</td>
<td>5.10</td>
<td>3.65</td>
<td>5.86</td>
</tr>
<tr>
<td>3_4</td>
<td>3.70</td>
<td>4.56</td>
<td>3.63</td>
<td>5.77</td>
</tr>
</tbody>
</table>

Table 5S.3. Average distances between compound 4 and selected MurD residues for the following monitored H-bond interactions: (a) ND1 nitrogen of His183 and oxygen of 4 amide (b) NE2 nitrogen of His183 and oxygen of 4 amide (c) backbone nitrogen of Thr36 and interacting moiety of compounds 4 (i) side chain oxygen of Thr36 and interacting moiety of compounds 4.

<table>
<thead>
<tr>
<th>Compound</th>
<th>His183 (1) [Å]</th>
<th>His183 (2) [Å]</th>
<th>Thr36 (N) [Å]</th>
<th>Thr36 (O)[Å]</th>
</tr>
</thead>
<tbody>
<tr>
<td>4_1</td>
<td>4.39</td>
<td>4.22</td>
<td>3.39</td>
<td>3.45</td>
</tr>
<tr>
<td>4_2</td>
<td>4.15</td>
<td>4.22</td>
<td>3.97</td>
<td>3.55</td>
</tr>
<tr>
<td>4_3</td>
<td>4.21</td>
<td>4.23</td>
<td>4.23</td>
<td>3.94</td>
</tr>
<tr>
<td>4_4</td>
<td>4.45</td>
<td>4.23</td>
<td>4.35</td>
<td>3.93</td>
</tr>
</tbody>
</table>
7. Average interactions energy values of compounds 2-4 for each independent MD simulation

**Table S6.** Average van der Waals and electrostatic interaction energy between MurD inhibitor 2-4 and their surrounding (solvated receptor P or aqueous solution W) obtained from MD simulations for full ligands for each independent 5ns MD simulation.

<table>
<thead>
<tr>
<th>Compound</th>
<th>( \langle V^{vdW}_{L-P} \rangle ) [kcal/mol]</th>
<th>( \langle V^{vdW}_{L-W} \rangle ) [kcal/mol]</th>
<th>( \langle V^{el}_{L-P} \rangle ) [kcal/mol]</th>
<th>( \langle V^{el}_{L-W} \rangle ) [kcal/mol]</th>
</tr>
</thead>
<tbody>
<tr>
<td>2_1</td>
<td>-51.490</td>
<td>-19.736</td>
<td>-475.132</td>
<td>-471.524</td>
</tr>
<tr>
<td>2_2</td>
<td>-50.312</td>
<td>-20.050</td>
<td>-474.578</td>
<td>-469.710</td>
</tr>
<tr>
<td>2_3</td>
<td>-51.000</td>
<td>-19.022</td>
<td>-473.684</td>
<td>-491.152</td>
</tr>
<tr>
<td>2_4</td>
<td>-51.632</td>
<td>-19.206</td>
<td>-474.166</td>
<td>-478.380</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Compound</th>
<th>( \langle V^{vdW}_{L-P} \rangle ) [kcal/mol]</th>
<th>( \langle V^{vdW}_{L-W} \rangle ) [kcal/mol]</th>
<th>( \langle V^{el}_{L-P} \rangle ) [kcal/mol]</th>
<th>( \langle V^{el}_{L-W} \rangle ) [kcal/mol]</th>
</tr>
</thead>
<tbody>
<tr>
<td>3_1</td>
<td>-54.280</td>
<td>-21.472</td>
<td>-474.016</td>
<td>-469.518</td>
</tr>
<tr>
<td>3_2</td>
<td>-54.928</td>
<td>-22.100</td>
<td>-478.936</td>
<td>-470.474</td>
</tr>
<tr>
<td>3_3</td>
<td>-56.162</td>
<td>-22.338</td>
<td>-480.346</td>
<td>-470.938</td>
</tr>
<tr>
<td>3_4</td>
<td>-55.698</td>
<td>-21.724</td>
<td>-473.342</td>
<td>-474.104</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Compound</th>
<th>( \langle V^{vdW}_{L-P} \rangle ) [kcal/mol]</th>
<th>( \langle V^{vdW}_{L-W} \rangle ) [kcal/mol]</th>
<th>( \langle V^{el}_{L-P} \rangle ) [kcal/mol]</th>
<th>( \langle V^{el}_{L-W} \rangle ) [kcal/mol]</th>
</tr>
</thead>
<tbody>
<tr>
<td>4_1</td>
<td>-57.368</td>
<td>-24.978</td>
<td>-444.268</td>
<td>-433.994</td>
</tr>
<tr>
<td>4_2</td>
<td>-59.496</td>
<td>-24.846</td>
<td>-447.072</td>
<td>-435.316</td>
</tr>
<tr>
<td>4_3</td>
<td>-58.864</td>
<td>-24.852</td>
<td>-443.734</td>
<td>-434.408</td>
</tr>
<tr>
<td>4_4</td>
<td>-58.014</td>
<td>-25.058</td>
<td>-444.360</td>
<td>-434.384</td>
</tr>
</tbody>
</table>
8. Average interactions energy values of the decomposed moieties of compounds 2-4 for each independent MD simulation

**Table S7.** Average van der Waals and electrostatic interaction energy between MurD inhibitors 2-4 and their surrounding (solvated receptor P or aqueous solution W) obtained from MD simulations for moiety 1.*

<table>
<thead>
<tr>
<th>Compound</th>
<th>$\langle V_{L-P}^{vdW}\rangle$ [kcal/mol]</th>
<th>$\langle V_{L-W}^{vdW}\rangle$ [kcal/mol]</th>
<th>$\langle V_{L-P}^{vdW}\rangle - \langle V_{L-W}^{vdW}\rangle$ [kcal/mol]</th>
<th>$\langle V_{L-P}^{el}\rangle$ [kcal/mol]</th>
<th>$\langle V_{L-W}^{el}\rangle$ [kcal/mol]</th>
<th>$\langle V_{L-P}^{el}\rangle - \langle V_{L-W}^{el}\rangle$ [kcal/mol]</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>-5.1±0.4</td>
<td>8.4±0.1</td>
<td>-13.4±0.5</td>
<td>-374.5±0.7</td>
<td>-370.7±2.6</td>
<td>-3.8±3.3</td>
</tr>
<tr>
<td>3</td>
<td>-5.9±0.4</td>
<td>8.1±0.1</td>
<td>-14.0±0.5</td>
<td>-384.5±2.3</td>
<td>-377.4±1.2</td>
<td>-7.1±3.5</td>
</tr>
<tr>
<td>4</td>
<td>-12.6±0.7</td>
<td>2.3±0.1</td>
<td>-14.9±0.8</td>
<td>-390.1±1.5</td>
<td>-377.5±0.5</td>
<td>-12.6±2.0</td>
</tr>
</tbody>
</table>

*Standard deviations were calculated from four 5 ns MD simulations, which were initiated from four independent starting configurations.

**Table S7.1.** Average van der Waals and electrostatic interaction energy between MurD inhibitor 2 and its surrounding (solvated receptor P or aqueous solution W) obtained from MD simulations for moiety 1 for each independent 5ns MD simulation.

<table>
<thead>
<tr>
<th>Compound</th>
<th>$\langle V_{L-P}^{vdW}\rangle$ [kcal/mol]</th>
<th>$\langle V_{L-W}^{vdW}\rangle$ [kcal/mol]</th>
<th>$\langle V_{L-P}^{el}\rangle$ [kcal/mol]</th>
<th>$\langle V_{L-W}^{el}\rangle$ [kcal/mol]</th>
</tr>
</thead>
<tbody>
<tr>
<td>4_1</td>
<td>-5.594</td>
<td>8.260</td>
<td>-383.306</td>
<td>-375.904</td>
</tr>
<tr>
<td>4_2</td>
<td>-6.564</td>
<td>8.090</td>
<td>-385.726</td>
<td>-377.032</td>
</tr>
<tr>
<td>4_3</td>
<td>-5.868</td>
<td>7.998</td>
<td>-387.136</td>
<td>-378.002</td>
</tr>
<tr>
<td>4_4</td>
<td>-5.700</td>
<td>8.224</td>
<td>-381.958</td>
<td>-378.788</td>
</tr>
</tbody>
</table>
Table S7.2. Average van der Waals and electrostatic interaction energy between MurD inhibitor 3 and its surrounding (solvated receptor P or aqueous solution W) obtained from MD simulations for moiety 1 for each independent 5ns MD simulation.

<table>
<thead>
<tr>
<th>Compound</th>
<th>$\langle V_{L-P}^{vdW} \rangle$ [kcal/mol]</th>
<th>$\langle V_{L-W}^{vdW} \rangle$ [kcal/mol]</th>
<th>$\langle V_{L-P}^{el} \rangle$ [kcal/mol]</th>
<th>$\langle V_{L-W}^{el} \rangle$ [kcal/mol]</th>
</tr>
</thead>
<tbody>
<tr>
<td>3_1</td>
<td>-5.206</td>
<td>8.348</td>
<td>-375.574</td>
<td>-373.364</td>
</tr>
<tr>
<td>3_2</td>
<td>-4.674</td>
<td>8.206</td>
<td>-373.986</td>
<td>-370.088</td>
</tr>
<tr>
<td>3_3</td>
<td>-4.914</td>
<td>8.704</td>
<td>-374.172</td>
<td>-381.824</td>
</tr>
<tr>
<td>3_4</td>
<td>-5.600</td>
<td>8.492</td>
<td>-374.438</td>
<td>-375.332</td>
</tr>
</tbody>
</table>

Table S7.3. Average van der Waals and electrostatic interaction energy between MurD inhibitor 4 and its surrounding (solvated receptor P or aqueous solution W) obtained from MD simulations for moiety 1 for each independent 5ns MD simulation.

<table>
<thead>
<tr>
<th>Compound</th>
<th>$\langle V_{L-P}^{vdW} \rangle$ [kcal/mol]</th>
<th>$\langle V_{L-W}^{vdW} \rangle$ [kcal/mol]</th>
<th>$\langle V_{L-P}^{el} \rangle$ [kcal/mol]</th>
<th>$\langle V_{L-W}^{el} \rangle$ [kcal/mol]</th>
</tr>
</thead>
<tbody>
<tr>
<td>4_1</td>
<td>-12.026</td>
<td>2.300</td>
<td>-389.578</td>
<td>-377.154</td>
</tr>
<tr>
<td>4_2</td>
<td>-13.520</td>
<td>2.388</td>
<td>-392.128</td>
<td>-378.290</td>
</tr>
<tr>
<td>4_3</td>
<td>-12.782</td>
<td>2.270</td>
<td>-388.706</td>
<td>-377.304</td>
</tr>
<tr>
<td>4_4</td>
<td>-12.206</td>
<td>2.308</td>
<td>-390.026</td>
<td>-377.338</td>
</tr>
</tbody>
</table>
Table S8. Average van der Waals and electrostatic interaction energy between MurD inhibitors 2-4 and their surrounding (solvated receptor P or aqueous solution W) obtained from MD simulations for moiety 2.*

<table>
<thead>
<tr>
<th>Compound</th>
<th>(\langle V_{vdW}^{L-P} \rangle) [kcal/mol]</th>
<th>(\langle V_{vdW}^{L-W} \rangle) [kcal/mol]</th>
<th>(\langle V_{cd}^{L-P} \rangle) [kcal/mol]</th>
<th>(\langle V_{cd}^{L-W} \rangle) [kcal/mol]</th>
<th>(\langle V_{cd}^{L-P} \rangle - \langle V_{cd}^{L-W} \rangle) [kcal/mol]</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>-3.4±0.4</td>
<td>-1.4±0.1</td>
<td>-2.0±0.5</td>
<td>-59.6±1.3</td>
<td>-55.4±0.6</td>
</tr>
<tr>
<td>3</td>
<td>-6.2±0.5</td>
<td>-2.7±0.1</td>
<td>-3.5±0.6</td>
<td>-39.2±0.6</td>
<td>-37.9±0.1</td>
</tr>
<tr>
<td>4</td>
<td>-3.2±0.1</td>
<td>-1.3±0.1</td>
<td>-1.9±0.2</td>
<td>-61.5±0.4</td>
<td>-60.0±3.4</td>
</tr>
</tbody>
</table>

*Standard deviations were calculated from four 5 ns MD simulations, which were initiated from four independent starting configurations.

Table S8.1. Average van der Waals and electrostatic interaction energy between MurD inhibitor 2 and its surrounding (solvated receptor P or aqueous solution W) obtained from MD simulations for moiety 2 for each independent 5ns MD simulation.

<table>
<thead>
<tr>
<th>Compound</th>
<th>(\langle V_{vdW}^{L-P} \rangle) [kcal/mol]</th>
<th>(\langle V_{vdW}^{L-W} \rangle) [kcal/mol]</th>
<th>(\langle V_{cd}^{L-P} \rangle) [kcal/mol]</th>
<th>(\langle V_{cd}^{L-W} \rangle) [kcal/mol]</th>
</tr>
</thead>
<tbody>
<tr>
<td>2_1</td>
<td>-3.226</td>
<td>-1.382</td>
<td>-61.474</td>
<td>-56.548</td>
</tr>
<tr>
<td>2_2</td>
<td>-3.028</td>
<td>-1.418</td>
<td>-62.132</td>
<td>-58.770</td>
</tr>
<tr>
<td>2_3</td>
<td>-3.298</td>
<td>-1.266</td>
<td>-61.118</td>
<td>-64.726</td>
</tr>
<tr>
<td>2_4</td>
<td>-3.190</td>
<td>-1.344</td>
<td>-61.416</td>
<td>-60.108</td>
</tr>
</tbody>
</table>
Table S8.2. Average van der Waals and electrostatic interaction energy between MurD inhibitor 4 and its surrounding (solvated receptor P or aqueous solution W) obtained from MD simulations for moiety 2 for each independent 5ns MD simulation.

<table>
<thead>
<tr>
<th>Compound</th>
<th>$\langle V_{vdW}^{L-P} \rangle$ [kcal/mol]</th>
<th>$\langle V_{vdW}^{L-W} \rangle$ [kcal/mol]</th>
<th>$\langle V_{el}^{L-P} \rangle$ [kcal/mol]</th>
<th>$\langle V_{el}^{L-W} \rangle$ [kcal/mol]</th>
</tr>
</thead>
<tbody>
<tr>
<td>3_1</td>
<td>-3.912</td>
<td>-1.462</td>
<td>-58.070</td>
<td>-54.680</td>
</tr>
<tr>
<td>3_2</td>
<td>-2.956</td>
<td>-1.512</td>
<td>-60.624</td>
<td>-55.800</td>
</tr>
<tr>
<td>3_3</td>
<td>-3.444</td>
<td>-1.518</td>
<td>-60.676</td>
<td>-55.104</td>
</tr>
<tr>
<td>3_4</td>
<td>-3.366</td>
<td>-1.462</td>
<td>-58.878</td>
<td>-55.872</td>
</tr>
</tbody>
</table>

Table S8.3. Average van der Waals and electrostatic interaction energy between MurD inhibitor 4 and its surrounding (solvated receptor P or aqueous solution W) obtained from MD simulations for moiety 2 for each independent 5ns MD simulation.

<table>
<thead>
<tr>
<th>Compound</th>
<th>$\langle V_{vdW}^{L-P} \rangle$ [kcal/mol]</th>
<th>$\langle V_{vdW}^{L-W} \rangle$ [kcal/mol]</th>
<th>$\langle V_{el}^{L-P} \rangle$ [kcal/mol]</th>
<th>$\langle V_{el}^{L-W} \rangle$ [kcal/mol]</th>
</tr>
</thead>
<tbody>
<tr>
<td>4_2</td>
<td>-5.608</td>
<td>-2.760</td>
<td>-39.414</td>
<td>-37.860</td>
</tr>
<tr>
<td>4_3</td>
<td>-5.918</td>
<td>-2.708</td>
<td>-39.736</td>
<td>-37.904</td>
</tr>
<tr>
<td>4_4</td>
<td>-6.648</td>
<td>-2.732</td>
<td>-38.418</td>
<td>-38.026</td>
</tr>
</tbody>
</table>
Table S9. Average van der Waals and electrostatic interaction energy between MurD inhibitors 2-4 and its surrounding (solvated receptor P or aqueous solution W) obtained from MD simulations for moiety 3.*

<table>
<thead>
<tr>
<th>Compound</th>
<th>$\langle V_{vdW}^{L-P} \rangle$ [kcal/mol]</th>
<th>$\langle V_{vdW}^{L-W} \rangle$ [kcal/mol]</th>
<th>$\langle V_{vdW}^{L-P} \rangle - \langle V_{vdW}^{L-W} \rangle$ [kcal/mol]</th>
<th>$\langle V_{el}^{L-P} \rangle$ [kcal/mol]</th>
<th>$\langle V_{el}^{L-W} \rangle$ [kcal/mol]</th>
<th>$\langle V_{el}^{L-P} \rangle - \langle V_{el}^{L-W} \rangle$ [kcal/mol]</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>-22.9±0.1</td>
<td>-17.5±0.1</td>
<td>-5.4±0.2</td>
<td>-2.2±0.3</td>
<td>-5.4±1.0</td>
<td>3.2±1.3</td>
</tr>
<tr>
<td>3</td>
<td>-26.4±0.3</td>
<td>-18.1±0.2</td>
<td>-8.3±0.5</td>
<td>1.4±0.2</td>
<td>-4.6±0.5</td>
<td>6.0±0.7</td>
</tr>
<tr>
<td>4</td>
<td>-15.8±0.3</td>
<td>-11.7±0.1</td>
<td>-4.1±0.4</td>
<td>10.6±0.2</td>
<td>7.2±0.1</td>
<td>3.4±0.3</td>
</tr>
</tbody>
</table>

*Standard deviations were calculated from four 5 ns MD simulations, which were initiated from four independent starting configurations.

Table S9.1. Average van der Waals and electrostatic interaction energy between MurD inhibitor 2 and its surrounding (solvated receptor P or aqueous solution W) obtained from MD simulations for moiety 3 for each independent 5ns MD simulation.

<table>
<thead>
<tr>
<th>Compound</th>
<th>$\langle V_{vdW}^{L-P} \rangle$ [kcal/mol]</th>
<th>$\langle V_{vdW}^{L-W} \rangle$ [kcal/mol]</th>
<th>$\langle V_{el}^{L-P} \rangle$ [kcal/mol]</th>
<th>$\langle V_{el}^{L-W} \rangle$ [kcal/mol]</th>
</tr>
</thead>
<tbody>
<tr>
<td>2_1</td>
<td>-23.034</td>
<td>-17.610</td>
<td>-2.352</td>
<td>-4.634</td>
</tr>
<tr>
<td>2_2</td>
<td>-22.800</td>
<td>-17.682</td>
<td>-1.950</td>
<td>-4.936</td>
</tr>
<tr>
<td>2_3</td>
<td>-22.714</td>
<td>-17.434</td>
<td>-2.534</td>
<td>-6.838</td>
</tr>
<tr>
<td>2_4</td>
<td>-22.900</td>
<td>-17.416</td>
<td>-2.038</td>
<td>-5.274</td>
</tr>
</tbody>
</table>
Table S9.2. Average van der Waals and electrostatic interaction energy between MurD inhibitor 3 and its surrounding (solvated receptor P or aqueous solution W) obtained from MD simulations for moiety 3 for each independent 5ns MD simulation.*

<table>
<thead>
<tr>
<th>Compound</th>
<th>( \langle V_{vdW}^{P} \rangle ) [kcal/mol]</th>
<th>( \langle V_{vdW}^{W} \rangle ) [kcal/mol]</th>
<th>( \langle V_{el}^{P} \rangle ) [kcal/mol]</th>
<th>( \langle V_{el}^{W} \rangle ) [kcal/mol]</th>
</tr>
</thead>
<tbody>
<tr>
<td>3_1</td>
<td>-25.824</td>
<td>-17.876</td>
<td>1.518</td>
<td>-3.898</td>
</tr>
<tr>
<td>3_2</td>
<td>-27.004</td>
<td>-18.128</td>
<td>1.632</td>
<td>-4.784</td>
</tr>
<tr>
<td>3_3</td>
<td>-26.850</td>
<td>-18.284</td>
<td>1.252</td>
<td>-4.452</td>
</tr>
<tr>
<td>3_4</td>
<td>-26.060</td>
<td>-18.044</td>
<td>1.308</td>
<td>-5.054</td>
</tr>
</tbody>
</table>

Table S9.3. Average van der Waals and electrostatic interaction energy between MurD inhibitor 4 and its surrounding (solvated receptor P or aqueous solution W) obtained from MD simulations for moiety 3 for each independent 5ns MD simulation.

<table>
<thead>
<tr>
<th>Compound</th>
<th>( \langle V_{vdW}^{P} \rangle ) [kcal/mol]</th>
<th>( \langle V_{vdW}^{W} \rangle ) [kcal/mol]</th>
<th>( \langle V_{el}^{P} \rangle ) [kcal/mol]</th>
<th>( \langle V_{el}^{W} \rangle ) [kcal/mol]</th>
</tr>
</thead>
<tbody>
<tr>
<td>4_1</td>
<td>-15.494</td>
<td>-11.754</td>
<td>10.400</td>
<td>7.260</td>
</tr>
<tr>
<td>4_2</td>
<td>-16.120</td>
<td>-11.64</td>
<td>10.588</td>
<td>7.050</td>
</tr>
<tr>
<td>4_3</td>
<td>-15.930</td>
<td>-11.702</td>
<td>10.556</td>
<td>7.326</td>
</tr>
<tr>
<td>4_4</td>
<td>-15.782</td>
<td>-11.778</td>
<td>10.874</td>
<td>7.190</td>
</tr>
</tbody>
</table>
Table S10. Average van der Waals and electrostatic interaction energy between MurD inhibitors 2-4 and their surrounding (solvated receptor P or aqueous solution W) obtained from MD simulations for moiety 4.*

<table>
<thead>
<tr>
<th>Compound</th>
<th>$\langle V_{vdW}^{P_L} \rangle$ [kcal/mol]</th>
<th>$\langle V_{vdW}^{W_L} \rangle$ [kcal/mol]</th>
<th>$\langle V_{vdW}^{vdW}<em>{L-P} \rangle - \langle V</em>{vdW}^{vdW}_{L-W} \rangle$ [kcal/mol]</th>
<th>$\langle V_{el}^{P_L} \rangle$ [kcal/mol]</th>
<th>$\langle V_{el}^{W_L} \rangle$ [kcal/mol]</th>
<th>$\langle V_{el}^{el}<em>{L-P} \rangle - \langle V</em>{el}^{el}_{L-W} \rangle$ [kcal/mol]</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>-20.0±0.1</td>
<td>-9.1±0.1</td>
<td>-10.9±0.2</td>
<td>-36.1±0.4</td>
<td>-37.1±0.8</td>
<td>1.0±1.2</td>
</tr>
<tr>
<td>3</td>
<td>-20.4±0.3</td>
<td>-10.5±0.1</td>
<td>-9.9±0.4</td>
<td>-34.0±0.2</td>
<td>-33.9±1.0</td>
<td>-0.1±1.2</td>
</tr>
<tr>
<td>4</td>
<td>-23.8±0.5</td>
<td>-12.8±0.1</td>
<td>-11.0±0.6</td>
<td>-26.1±0.5</td>
<td>-26.3±0.2</td>
<td>0.2±0.7</td>
</tr>
</tbody>
</table>

*Standard deviations were calculated from four 5 ns MD simulations, which were initiated from four independent starting configurations.

Table S10.1. Average van der Waals and electrostatic interaction energy between MurD inhibitor 2 and its surrounding (solvated receptor P or aqueous solution W) obtained from MD simulations for moiety 4 for each independent 5ns MD simulation.

<table>
<thead>
<tr>
<th>Compound</th>
<th>$\langle V_{vdW}^{P_L} \rangle$ [kcal/mol]</th>
<th>$\langle V_{vdW}^{W_L} \rangle$ [kcal/mol]</th>
<th>$\langle V_{el}^{P_L} \rangle$ [kcal/mol]</th>
<th>$\langle V_{el}^{W_L} \rangle$ [kcal/mol]</th>
<th>$\langle V_{el}^{el}_{L-P} \rangle$ [kcal/mol]</th>
</tr>
</thead>
<tbody>
<tr>
<td>2_1</td>
<td>-20.024</td>
<td>-9.092</td>
<td>-35.732</td>
<td>-36.978</td>
<td></td>
</tr>
<tr>
<td>2_2</td>
<td>-19.810</td>
<td>-9.156</td>
<td>-36.510</td>
<td>-35.916</td>
<td></td>
</tr>
<tr>
<td>2_3</td>
<td>-20.074</td>
<td>-9.026</td>
<td>-35.860</td>
<td>-37.764</td>
<td></td>
</tr>
<tr>
<td>2_4</td>
<td>-19.942</td>
<td>-8.938</td>
<td>-36.274</td>
<td>-37.666</td>
<td></td>
</tr>
</tbody>
</table>
Table S10.2. Average van der Waals and electrostatic interaction energy between MurD inhibitor 3 and its surrounding (solvated receptor P or aqueous solution W) obtained from MD simulations for moiety 4 for each independent 5ns MD simulation.

<table>
<thead>
<tr>
<th>Compound</th>
<th>$\langle V_{vdW}^{L-P} \rangle$ [kcal/mol]</th>
<th>$\langle V_{vdW}^{L-W} \rangle$ [kcal/mol]</th>
<th>$\langle V_{el}^{L-P} \rangle$ [kcal/mol]</th>
<th>$\langle V_{el}^{L-W} \rangle$ [kcal/mol]</th>
</tr>
</thead>
<tbody>
<tr>
<td>3_1</td>
<td>-19.918</td>
<td>-10.394</td>
<td>-34.158</td>
<td>-35.036</td>
</tr>
<tr>
<td>3_2</td>
<td>-20.722</td>
<td>-10.550</td>
<td>-34.218</td>
<td>-32.858</td>
</tr>
<tr>
<td>3_3</td>
<td>-20.468</td>
<td>-10.534</td>
<td>-33.786</td>
<td>-33.380</td>
</tr>
<tr>
<td>3_4</td>
<td>-20.372</td>
<td>-10.442</td>
<td>-33.814</td>
<td>-34.390</td>
</tr>
</tbody>
</table>

Table S10.3. Average van der Waals and electrostatic interaction energy between MurD inhibitor 4 and its surrounding (solvated receptor P or aqueous solution W) obtained from MD simulations for moiety 4 for each independent 5ns MD simulation.

<table>
<thead>
<tr>
<th>Compound</th>
<th>$\langle V_{vdW}^{L-P} \rangle$ [kcal/mol]</th>
<th>$\langle V_{vdW}^{L-W} \rangle$ [kcal/mol]</th>
<th>$\langle V_{el}^{L-P} \rangle$ [kcal/mol]</th>
<th>$\langle V_{el}^{L-W} \rangle$ [kcal/mol]</th>
</tr>
</thead>
<tbody>
<tr>
<td>4_1</td>
<td>-23.358</td>
<td>-12.802</td>
<td>-25.802</td>
<td>-26.136</td>
</tr>
<tr>
<td>4_4</td>
<td>-23.378</td>
<td>-12.856</td>
<td>-26.79</td>
<td>-26.210</td>
</tr>
</tbody>
</table>
9. Time-dependent distances between selected LIGAND-PROTEIN atoms

**Compound 2**

![Graph](image)

**Figure 4S(A).** Time dependence of distance between side chain oxygen of Thr321 and first carboxylic (α) oxygen of compound 2. Each plotted 5000 ps represent one independent MD simulation.

![Graph](image)

**Figure 4S(B).** Time dependence of distance between side chain nitrogen of Lys348 and first carboxylic (α) oxygen of compound 2. Each plotted 5000 ps represent one independent MD simulation.
Figure 4S(C). Time dependence of distance between backbone nitrogen of Ser415 and second carboxylic (γ) oxygen of compound 2. Each plotted 5000 ps represent one independent MD simulation.

Figure 4S(D). Time dependence of distance between side chain oxygen of Ser415 and second carboxylic (γ) oxygen of compound 2. Each plotted 5000 ps represent one independent MD simulation.
Figure 4S(E). Time dependence of distance between backbone nitrogen of Phe422 and second carboxylic (γ) oxygen of compound 2. Each plotted 5000 ps represent one independent MD simulation.

Figure 4S(F). Time dependence of distance between nitrogen (ND1) of His183 and moiety oxo oxygen of compound 2. Each plotted 5000 ps represent one independent MD simulation.
**Figure 4S(G).** Time dependence of distance between nitrogen (NE2) of His183 and oxo oxygen of compound 2. Each plotted 5000 ps represent one independent MD simulation.

**Figure 4S(H).** Time dependence of distance between chain oxygen of Thr36 and rhodanine nitrogen of compound 2. Each plotted 5000 ps represent one independent MD simulation.
Figure 4S(1). Time dependence of distance between chain nitrogen of Thr36 and oxo rhodanine oxygen of compound 2. Each plotted 5000 ps represent one independent MD simulation.
Compound 3

**Figure 5S(A).** Time dependence of distance between side chain oxygen of Thr321 and first carboxylic ($\alpha$) oxygen of compound 3. Each plotted 5000 ps represent one independent MD simulation.

**Figure 5S(B).** Time dependence of distance between side chain nitrogen of Lys348 and first carboxylic ($\alpha$) oxygen of compound 3. Each plotted 5000 ps represent one independent MD simulation.
Figure 5S(C). Time dependence of distance between backbone nitrogen of Ser415 and second carboxylic ($\gamma$) oxygen of compound 3. Each plotted 5000 ps represent one independent MD simulation.

Figure 5S(D). Time dependence of distance between side chain oxygen of Ser415 and second carboxylic ($\gamma$) oxygen of compound 3. Each plotted 5000 ps represent one independent MD simulation.
**Figure 5S(E).** Time dependence of distance between backbone nitrogen of Phe422 and second carboxylic (γ) oxygen of compound 3. Each plotted 5000 ps represent one independent MD simulation.

**Figure 5S(F).** Time dependence of distance between nitrogen (ND1) of His183 and oxo oxygen of compound 3. Each plotted 5000 ps represent one independent MD simulation.
**Figure 5S(G).** Time dependence of distance between nitrogen (NE2) of His183 and oxo oxygen of compound 3. Each plotted 5000 ps represent one independent MD simulation.

**Figure 5S(H).** Time dependence of distance between nitrogen of Thr36 and rhodanine sulfur of compound 3. Each plotted 5000 ps represent one independent MD simulation.
Figure 5S(I). Time dependence of distance between chain oxygen of Thr36 and rhodanine nitrogen of compound 3. Each plotted 5000 ps represent one independent MD simulation.
**Compound 4**

![Graph A](image1.png)

**Figure 6S(A).** Time dependence of distance between side chain oxygen of Thr321 and first carboxylic oxygen of compound 4. Each plotted 5000 ps represent one independent MD simulation.

![Graph B](image2.png)

**Figure 6S(B).** Time dependence of distance between side chain nitrogen of Lys348 and first carboxylic oxygen of compound 4. Each plotted 5000 ps represent one independent MD simulation.
**Figure 6S(C).** Time dependence of distance between backbone nitrogen of Ser415 and second carboxylic oxygen of compound 4. Each plotted 5000 ps represent one independent MD simulation.

**Figure 6S(D).** Time dependence of distance between side chain oxygen of Ser415 and second carboxylic oxygen of compound 4. Each plotted 5000 ps represent one independent MD simulation.
Figure 6S(E). Time dependence of distance between backbone nitrogen of Phe422 and second carboxylic oxygen of compound 4. Each plotted 5000 ps represent one independent MD simulation.

Figure 6S(F). Time dependence of distance between nitrogen (ND1) of His183 and sulfonamide moiety oxygen of compound 4. Each plotted 5000 ps represent one independent MD simulation.
Figure 6S(G). Time dependence of distance between nitrogen (NE2) of His183 and sulfonamide moiety oxygen of compound 4. Each plotted 5000 ps represent one independent MD simulation.

Figure 6S(H). Time dependence of distance between chain nitrogen of Thr36 and ciano group of compound 4. Each plotted 5000 ps represent one independent MD simulation.
Figure 6S(I). Time dependence of distance between chain oxygen of Thr36 and ciano group of compound 4. Each plotted 5000 ps represent one independent MD simulation.
10. Calculated GRID contour surface for the water probe

Fig. 7S. Calculated GRID contour surfaces of the water probe at -6.0 kcal/mol in the MurD binding site. Compound 1 from the 2JJF crystal structure is indicated for better visualization of the MurD binding site.