# Supplementary Information

## Flavonoids as putative epi-modulators: Insights into their binding mode with BRD4 bromodomain using molecular docking and dynamics.

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**Table S1.** BRD4 PDBIDs used for cross-docking studies

| *ID* | *Resolution(Å)* | *R-factor* |
|---|---|---|
| *3MXF* | 1.6 | 0.184 |
| *3P5O* | 1.6 | 0.185 |
| *3U5L* | 1.39 | 0.142 |
| *4LYW* | 1.95 | 0.235 |
| *4MR4* | 1.66 | 0.194 |
| *4NUD* | 1.2 | 0.171 |
| *4XYA* | 2.05 | 0.207 |
| *4YH3* | 1.6 | 0.199 |
| *5KJ0* | 1.51 | 0.17 |
| *5M3A* | 1.65 | 0.214 |
| *5TI2* | 1.65 | 0.181 |
| *5TI3* | 1.703 | 0.194 |
| *5U28* | 1.798 | 0.223 |
| *5VOM* | 1.67 | 0.218 |

**Table S2.** $IC_{50}$ and experimental binding energy values and of reference ligands for BRD4 inhibition as reported on the literature.

| Ligand | $IC_{50}$ (nM) | ΔG (kcal/mol) |
|---|---|---|
| **JQ-1** | **60** | **-9.64** |
| **Molibresib** | **40** | **N/A** |
| **BZT-7** | **640** | **-8.16** |
| **XD14** | **N/A** | **-9.0** |
| **RVX-208** | **645** | **-7.84** |
| **MS436** | **~4000** | **N/A** |
| **43S** | **N/A** | **-7.73** |
| **CHEMBL3589468** | **9000** | **N/A** |
| **6TB** | **130** | **N/A** |
| **7E7** | **2000** | **N/A** |
| **ZINC5329468** | **240** | **N/A** |
| **7CG** | **44** | **N/A** |
| **SF2523** | **240** | **N/A** |
| **9GY** | **790** | **N/A** |

**Table S3.** Scoring values for reference ligands as obtained by the docking software used herein.

| MOLECULE | SUMMARY STATS | AUTODOCK VINA | LEDOCK | MOE | PLANTS |
|---|---|---|---|---|---|
| **JQ-1** | Min: | -9.0 kcal/mol | -5.9 kcal/mol | -8.5 kcal/mol | -102.1 |
| | 1st Quart.: | -7.6 kcal/mol | -5.5 kcal/mol | -7.4 kcal/mol | -80.7 |
| | Avg: | -7.3 kcal/mol | -5.0 kcal/mol | -6.9 kcal/mol | -74.0 |
| | 3rd Quart.: | -6.8 kcal/mol | -4.5 kcal/mol | -6.4 kcal/mol | -68.0 |
| | Max: | -5.8 kcal/mol | -4.2 kcal/mol | -5.3 kcal/mol | -50.4 |
| | SD: | 0.7 kcal/mol | 0.6 kcal/mol | 0.7 kcal/mol | 11.8 |

| | | | | | |
|---|---|---|---|---|---|
| **MOLIBRESIB** | Min: | -9.3 kcal/mol | -6.3 kcal/mol | -8.3 kcal/mol | -102.8 |
| | 1st Quart.: | -8.2 kcal/mol | -6.2 kcal/mol | -7.4 kcal/mol | -83.2 |
| | Avg: | -7.6 kcal/mol | -5.7 kcal/mol | -6.9 kcal/mol | -75.6 |
| | 3rd Quart.: | -7.1 kcal/mol | -5.3 kcal/mol | -6.4 kcal/mol | -67.8 |
| | Max: | -6.5 kcal/mol | -4.6 kcal/mol | -5.3 kcal/mol | -62.0 |
| | SD: | 0.7 kcal/mol | 0.5 kcal/mol | 0.7 kcal/mol | 10.3 |
| **BZT-7** | Min: | -9.3 kcal/mol | -5.5 kcal/mol | -7.2 kcal/mol | -92.8 |
| | 1st Quart.: | -8.0 kcal/mol | -4.9 kcal/mol | -6.0 kcal/mol | -77.6 |
| | Avg: | -7.7 kcal/mol | -4.5 kcal/mol | -5.6 kcal/mol | -72.2 |
| | 3rd Quart.: | -7.2 kcal/mol | -4.2 kcal/mol | -5.1 kcal/mol | -65.7 |
| | Max: | -6.3 kcal/mol | -3.7 kcal/mol | -4.3 kcal/mol | -50.6 |
| | SD: | 0.7 kcal/mol | 0.5 kcal/mol | 0.6 kcal/mol | 12.0 |
| **XD14** | Min: | -7.7 kcal/mol | -7.0 kcal/mol | -7.8 kcal/mol | -96.7 |
| | 1st Quart.: | -6.9 kcal/mol | -6.4 kcal/mol | -6.8 kcal/mol | -80.2 |
| | Avg: | -6.6 kcal/mol | -6.0 kcal/mol | -6.5 kcal/mol | -76.1 |
| | 3rd Quart.: | -6.3 kcal/mol | -5.8 kcal/mol | -6.2 kcal/mol | -71.7 |
| | Max: | -6.0 kcal/mol | -4.4 kcal/mol | -5.8 kcal/mol | -64.5 |
| | SD: | 0.4 kcal/mol | 0.4 kcal/mol | 0.4 kcal/mol | 7.0 |
| **RVX-208** | Min: | -7.7 kcal/mol | -6.5 kcal/mol | -7.2 kcal/mol | -69.4 |
| | 1st Quart.: | -7.0 kcal/mol | -6.0 kcal/mol | -6.5 kcal/mol | -61.8 |
| | Avg: | -6.8 kcal/mol | -5.6 kcal/mol | -6.2 kcal/mol | -57.4 |
| | 3rd Quart.: | -6.7 kcal/mol | -5.3 kcal/mol | -5.9 kcal/mol | -52.2 |
| | Max: | -6.4 kcal/mol | -4.5 kcal/mol | -5.6 kcal/mol | -46.4 |
| | SD: | 0.2 kcal/mol | 0.4 kcal/mol | 0.4 kcal/mol | 6.2 |
| **MS436** | Min: | -9.0 kcal/mol | -6.6 kcal/mol | -6.8 kcal/mol | -84.4 |
| | 1st Quart.: | -8.2 kcal/mol | -6.1 kcal/mol | -6.2 kcal/mol | -79.7 |
| | Avg: | -8.0 kcal/mol | -6.0 kcal/mol | -5.9 kcal/mol | -75.9 |
| | 3rd Quart.: | -7.7 kcal/mol | -5.8 kcal/mol | -5.6 kcal/mol | -73.2 |
| | Max: | -7.3 kcal/mol | -5.3 kcal/mol | -5.1 kcal/mol | -64.9 |
| | SD: | 0.3 kcal/mol | 0.2 kcal/mol | 0.4 kcal/mol | 5.0 |
| **43S** | Min: | -8.8 kcal/mol | -6.4 kcal/mol | -7.0 kcal/mol | -74.5 |
| | 1st Quart.: | -8.1 kcal/mol | -6.1 kcal/mol | -6.0 kcal/mol | -71.0 |
| | Avg: | -7.7 kcal/mol | -5.8 kcal/mol | -5.7 kcal/mol | -68.3 |
| | 3rd Quart.: | -7.5 kcal/mol | -5.6 kcal/mol | -5.4 kcal/mol | -65.4 |
| | Max: | -6.7 kcal/mol | -5.1 kcal/mol | -4.7 kcal/mol | -62.9 |
| | SD: | 0.4 kcal/mol | 0.4 kcal/mol | 0.4 kcal/mol | 3.3 |
| **CHEMBL3589468** | Min: | -9.6 kcal/mol | -5.3 kcal/mol | -7.3 kcal/mol | -94.2 |
| | 1st Quart.: | -8.2 kcal/mol | -5.0 kcal/mol | -6.3 kcal/mol | -74.4 |
| | Avg: | -7.9 kcal/mol | -4.7 kcal/mol | -6.2 kcal/mol | -67.8 |
| | 3rd Quart.: | -7.6 kcal/mol | -4.4 kcal/mol | -5.9 kcal/mol | -61.2 |
| | Max: | -6.8 kcal/mol | -4.2 kcal/mol | -5.6 kcal/mol | -44.9 |
| | SD: | 0.5 kcal/mol | 0.3 kcal/mol | 0.3 kcal/mol | 11.0 |
| **6TB** | Min: | -8.3 kcal/mol | -6.3 kcal/mol | -9.4 kcal/mol | -63.2 |
| | 1st Quart.: | -7.0 kcal/mol | -5.7 kcal/mol | -7.4 kcal/mol | -51.3 |
| | Avg: | -6.8 kcal/mol | -5.4 kcal/mol | -7.1 kcal/mol | -46.3 |
| | 3rd Quart.: | -6.6 kcal/mol | -5.0 kcal/mol | -6.7 kcal/mol | -41.0 |
| | Max: | -6.1 kcal/mol | -4.4 kcal/mol | -6.1 kcal/mol | -34.8 |
| | SD: | 0.3 kcal/mol | 0.5 kcal/mol | 0.6 kcal/mol | 6.4 |

| | | | | | |
|---|---|---|---|---|---|
| **7E7** | Min: | -8.9 kcal/mol | -6.3 kcal/mol | -7.0 kcal/mol | -69.9 |
| | 1st Quart.: | -8.0 kcal/mol | -5.8 kcal/mol | -6.3 kcal/mol | -61.9 |
| | Avg: | -7.7 kcal/mol | -5.7 kcal/mol | -6.1 kcal/mol | -60.0 |
| | 3rd Quart.: | -7.4 kcal/mol | -5.4 kcal/mol | -5.8 kcal/mol | -57.3 |
| | Max: | -6.8 kcal/mol | -5.2 kcal/mol | -5.5 kcal/mol | -52.5 |
| | SD: | 0.4 kcal/mol | 0.3 kcal/mol | 0.3 kcal/mol | 4.2 |
| **ZINC5329468** | Min: | -8.6 kcal/mol | -5.5 kcal/mol | -6.8 kcal/mol | -80.0 |
| | 1st Quart.: | -8.0 kcal/mol | -4.9 kcal/mol | -6.2 kcal/mol | -75.9 |
| | Avg: | -7.7 kcal/mol | -4.7 kcal/mol | -6.0 kcal/mol | -73.7 |
| | 3rd Quart.: | -7.4 kcal/mol | -4.4 kcal/mol | -5.8 kcal/mol | -71.6 |
| | Max: | -6.9 kcal/mol | -4.0 kcal/mol | -5.4 kcal/mol | -65.8 |
| | SD: | 0.4 kcal/mol | 0.3 kcal/mol | 0.3 kcal/mol | 3.6 |
| **7CG** | Min: | -7.9 kcal/mol | -6.0 kcal/mol | -7.0 kcal/mol | -80.9 |
| | 1st Quart.: | -7.4 kcal/mol | -5.6 kcal/mol | -6.1 kcal/mol | -75.2 |
| | Avg: | -7.2 kcal/mol | -5.4 kcal/mol | -6.0 kcal/mol | -73.0 |
| | 3rd Quart.: | -7.0 kcal/mol | -5.3 kcal/mol | -5.7 kcal/mol | -70.6 |
| | Max: | -6.5 kcal/mol | -4.9 kcal/mol | -5.4 kcal/mol | -65.9 |
| | SD: | 0.2 kcal/mol | 0.3 kcal/mol | 0.3 kcal/mol | 3.7 |
| **SF2523** | Min: | -8.8 kcal/mol | -5.7 kcal/mol | -7.3 kcal/mol | -75.8 |
| | 1st Quart.: | -8.1 kcal/mol | -5.3 kcal/mol | -6.4 kcal/mol | -69.2 |
| | Avg: | -7.7 kcal/mol | -4.9 kcal/mol | -6.2 kcal/mol | -66.6 |
| | 3rd Quart.: | -7.4 kcal/mol | -4.5 kcal/mol | -6.0 kcal/mol | -63.0 |
| | Max: | -6.5 kcal/mol | -4.1 kcal/mol | -5.3 kcal/mol | -53.9 |
| | SD: | 0.4 kcal/mol | 0.5 kcal/mol | 0.3 kcal/mol | 4.6 |
| **9GY** | Min: | -10.3 kcal/mol | -5.7 kcal/mol | -8.2 kcal/mol | -105.5 |
| | 1st Quart.: | -9.2 kcal/mol | -5.2 kcal/mol | -7.2 kcal/mol | -96.2 |
| | Avg: | -8.8 kcal/mol | -5.0 kcal/mol | -6.9 kcal/mol | -85.6 |
| | 3rd Quart.: | -8.3 kcal/mol | -4.9 kcal/mol | -6.5 kcal/mol | -73.1 |
| | Max: | -7.7 kcal/mol | -4.5 kcal/mol | -5.8 kcal/mol | -54.4 |
| | SD: | 0.6 kcal/mol | 0.2 kcal/mol | 0.5 kcal/mol | 14.2 |

**Table S4.** Scoring values obtained with LeDock for amentoflavone per protein-ligand complex of the ensemble

| 3MXF | 3P5O | 3U5L | 4LYW | 4MR4 | 4NUD | 4XYA | 4YH3 | 5KJ0 | 5M3A | 5TI2 | 5TI3 | 5U28 | 5VOM |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| -7.4 | -7.7 | -7.7 | -7.5 | -7.4 | -7.3 | -7.4 | -7.0 | -7.4 | -7.7 | -7.7 | -7.9 | -7.4 | -7.3 |
| -7.4 | -7.7 | -7.4 | -7.3 | -7.4 | -7.3 | -7.2 | -6.8 | -7.3 | -7.7 | -7.5 | -7.4 | -7.3 | -7.0 |
| -7.2 | -7.4 | -7.3 | -7.3 | -7.3 | -7.2 | -7.0 | -6.8 | -7.2 | -7.5 | -7.5 | -7.4 | -7.1 | -6.8 |
| -7.0 | -7.2 | -6.8 | -7.2 | -7.1 | -7.2 | -6.9 | -6.8 | -7.2 | -7.4 | -7.4 | -7.3 | -7.1 | -6.8 |
| -7.0 | -7.1 | -6.8 | -7.0 | -7.0 | -7.2 | -6.8 | -6.7 | -7.1 | -7.4 | -7.4 | -7.1 | -7.0 | -6.5 |
| -6.9 | -7.1 | -6.7 | -6.9 | -7.0 | -7.2 | -6.8 | -6.7 | -7.0 | -7.3 | -7.3 | -6.9 | -6.8 | -6.4 |
| -6.6 | -6.9 | -6.7 | -6.9 | -6.9 | -7.0 | -6.5 | -6.6 | -7.0 | -7.2 | -7.3 | -6.9 | -6.7 | -6.4 |
| -6.5 | -6.9 | -6.6 | -6.8 | -6.8 | -7.0 | -6.5 | -6.5 | -6.9 | -7.2 | -7.2 | -6.8 | -6.6 | -6.4 |
| -6.4 | -6.9 | -6.6 | -6.7 | -6.8 | -7.0 | -6.5 | -6.5 | -6.8 | -7.1 | -7.0 | -6.8 | -6.5 | -6.3 |

**Table S5.** Scoring values obtained with MOE for amentoflavone per protein-ligand complex of the ensemble

| 3MXF | 3P5O | 3U5L | 4LYW | 4MR4 | 4NUD | 4XYA | 4YH3 | 5KJ0 | 5M3A | 5TI2 | 5TI3 | 5U28 | 5VOM |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| -8.8 | -8.4 | -8.0 | -8.5 | -7.8 | -8.4 | -9.0 | -8.3 | -8.2 | -8.0 | -7.8 | -7.8 | -8.8 | -8.6 |
| -8.7 | -8.0 | -8.0 | -7.6 | -7.5 | -8.4 | -8.3 | -8.2 | -8.2 | -7.9 | -7.5 | -7.8 | -8.4 | -8.4 |
| -8.0 | -7.6 | -7.3 | -7.5 | -7.3 | -8.3 | -8.2 | -7.8 | -8.1 | -7.9 | -7.4 | -7.4 | -8.3 | -8.2 |
| -7.9 | -7.4 | -7.3 | -7.3 | -7.3 | -7.6 | -8.0 | -7.8 | -8.1 | -7.5 | -7.4 | -7.3 | -8.2 | -8.2 |
| -7.8 | -7.4 | -7.2 | -7.2 | -7.3 | -7.4 | -7.8 | -7.8 | -8.1 | -7.4 | -7.2 | -7.1 | -8.2 | -8.0 |
| -7.7 | -7.4 | -7.2 | -7.0 | -7.0 | -7.0 | -7.5 | -7.8 | -7.8 | -7.3 | -7.0 | -7.1 | -7.9 | -7.7 |
| -7.4 | -7.2 | -7.1 | -7.0 | -6.8 | -6.9 | -7.4 | -7.7 | -7.8 | -7.2 | -7.0 | -7.0 | -7.9 | -7.7 |
| -7.4 | -7.2 | -7.0 | -6.8 | -6.6 | -6.7 | -7.4 | -7.5 | -7.3 | -7.0 | -7.0 | -7.0 | -7.8 | -7.7 |
| -7.2 | -7.0 | -6.8 | -6.5 | -6.4 | -6.6 | -7.1 | -7.4 | -7.3 | -7.0 | -6.7 | -6.7 | -7.4 | -7.5 |

**Table S6.** Scoring values obtained with PLANTS for amentoflavone per protein-ligand complex of the ensemble

| 3MXF | 3P5O | 3U5L | 4LYW | 4MR4 | 4NUD | 4XYA | 4YH3 | 5KJ0 | 5M3A | 5TI2 | 5TI3 | 5U28 | 5VOM |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| -94.4 | -94.9 | -93.5 | -98.5 | -92.4 | -91.6 | -89.4 | -92.8 | -93.8 | -102.1 | -92.8 | -98.0 | -93.3 | -84.5 |
| -89.4 | -94.3 | -89.6 | -96.7 | -91.4 | -91.0 | -87.3 | -91.1 | -93.4 | -101.1 | -91.2 | -91.5 | -89.1 | -82.8 |
| -88.8 | -90.8 | -86.4 | -89.3 | -89.0 | -90.5 | -85.5 | -91.0 | -90.6 | -96.6 | -87.7 | -90.0 | -88.9 | -80.8 |
| -87.4 | -86.2 | -85.1 | -88.4 | -88.0 | -89.5 | -84.7 | -90.8 | -87.4 | -95.1 | -87.4 | -85.3 | -88.7 | -79.7 |
| -87.2 | -85.4 | -84.2 | -86.8 | -86.3 | -88.4 | -84.5 | -90.2 | -86.1 | -94.3 | -85.8 | -85.1 | -87.3 | -78.0 |
| -86.8 | -85.0 | -83.6 | -86.7 | -86.0 | -87.6 | -84.4 | -89.2 | -84.0 | -90.7 | -82.6 | -85.0 | -87.0 | -78.0 |
| -86.8 | -84.6 | -83.4 | -86.6 | -85.9 | -85.8 | -84.2 | -87.5 | -83.8 | -90.6 | -81.8 | -85.0 | -85.7 | -77.9 |
| -84.9 | -84.5 | -82.7 | -86.6 | -84.6 | -85.2 | -83.2 | -87.4 | -83.7 | -88.3 | -81.8 | -84.0 | -85.6 | -77.8 |
| -83.3 | -82.7 | -82.6 | -84.4 | -84.2 | -84.0 | -83.0 | -84.4 | -83.3 | -86.3 | -81.0 | -83.8 | -85.2 | -77.6 |

**Table S7.** Scoring values obtained with Vina for amentoflavone per protein-ligand complex of the ensemble

| 3MXF | 3P5O | 3U5L | 4LYW | 4MR4 | 4NUD | 4XYA | 4YH3 | 5KJ0 | 5M3A | 5TI2 | 5TI3 | 5U28 | 5VOM |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| -9.9 | -10.2 | -9.7 | -10.1 | -9.5 | -10.0 | -9.6 | -9.6 | -9.8 | -10.0 | -10.5 | -10.5 | -9.5 | -9.5 |
| -9.5 | -10.0 | -9.6 | -10.0 | -9.5 | -10.0 | -9.5 | -9.4 | -9.5 | -9.9 | -9.5 | -10.0 | -9.4 | -9.0 |
| -9.5 | -9.4 | -9.4 | -9.9 | -9.5 | -10.0 | -9.4 | -9.3 | -9.3 | -9.9 | -9.4 | -9.8 | -9.3 | -8.9 |
| -9.4 | -9.3 | -9.4 | -9.6 | -9.4 | -9.9 | -9.2 | -9.3 | -9.2 | -9.8 | -9.4 | -9.4 | -9.2 | -8.4 |
| -9.4 | -9.2 | -9.1 | -9.5 | -9.3 | -9.5 | -9.2 | -9.3 | -9.2 | -9.5 | -9.1 | -9.1 | -9.0 | -8.4 |
| -9.4 | -9.0 | -9.0 | -9.5 | -9.2 | -9.2 | -9.0 | -9.2 | -8.9 | -9.5 | -9.1 | -9.0 | -9.0 | -8.3 |
| -9.3 | -9.0 | -9.0 | -9.3 | -9.1 | -9.1 | -8.8 | -9.0 | -8.6 | -9.5 | -9.0 | -9.0 | -8.7 | -8.2 |
| -9.3 | -8.9 | -8.8 | -9.3 | -9.0 | -8.7 | -8.7 | -8.9 | -8.4 | -9.5 | -9.0 | -9.0 | -8.5 | -8.2 |
| -9.2 | -8.7 | -8.8 | -9.2 | -8.9 | -8.7 | -8.7 | -8.9 | -8.3 | -9.4 | -8.8 | -8.9 | -8.5 | -8.2 |

**Table S8.** Scoring values obtained with LeDock for fisetin per protein-ligand complex of the ensemble

| 3MXF | 3P5O | 3U5L | 4LYW | 4MR4 | 4NUD | 4XYA | 4YH3 | 5KJ0 | 5M3A | 5TI2 | 5TI3 | 5U28 | 5VOM |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| -5.8 | -5.6 | -5.5 | -5.7 | -5.7 | -5.8 | -5.7 | -5.3 | -5.6 | -6.0 | -6.0 | -6.0 | -5.5 | -5.7 |
| -5.8 | -5.6 | -5.5 | -5.6 | -5.7 | -5.8 | -5.7 | -5.2 | -5.6 | -5.9 | -6.0 | -6.0 | -5.5 | -5.7 |
| -5.6 | -5.5 | -5.5 | -5.6 | -5.6 | -5.7 | -5.6 | -5.2 | -5.5 | -5.9 | -5.8 | -5.8 | -5.4 | -5.7 |
| -5.6 | -5.4 | -5.4 | -5.6 | -5.3 | -5.6 | -5.6 | -5.1 | -5.5 | -5.6 | -5.5 | -5.5 | -5.3 | -5.6 |
| -5.5 | -5.3 | -5.3 | -5.5 | -5.3 | -5.5 | -5.5 | -5.1 | -5.4 | -5.5 | -5.4 | -5.4 | -5.2 | -5.6 |
| -5.4 | -5.3 | -5.3 | -5.5 | -5.3 | -5.5 | -5.5 | -5.1 | -5.4 | -5.5 | -5.4 | -5.4 | -5.2 | -5.4 |
| -5.4 | -5.3 | -5.3 | -5.5 | -5.2 | -5.2 | -5.5 | -5.0 | -5.4 | -5.5 | -5.2 | -5.3 | -5.0 | -5.4 |
| -5.4 | -5.2 | -5.3 | -5.5 | -5.2 | -5.1 | -5.4 | -4.8 | -5.4 | -5.4 | -5.2 | -5.2 | -5.0 | -5.3 |
| -5.3 | -5.2 | -5.3 | -5.4 | -5.1 | -5.0 | -5.4 | -4.7 | -5.4 | -5.4 | -5.2 | -5.2 | -5.0 | -5.3 |

**Table S9.** Scoring values obtained with MOE for fisetin per protein-ligand complex of the ensemble

| 3MXF | 3P5O | 3U5L | 4LYW | 4MR4 | 4NUD | 4XYA | 4YH3 | 5KJ0 | 5M3A | 5TI2 | 5TI3 | 5U28 | 5VOM |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| -6.3 | -6.2 | -6.3 | -6.8 | -6.0 | -7.0 | -7.4 | -6.4 | -6.4 | -7.4 | -6.5 | -6.5 | -6.9 | -6.6 |
| -6.3 | -6.2 | -6.3 | -6.8 | -6.0 | -7.0 | -7.0 | -6.2 | -6.3 | -6.6 | -6.4 | -6.4 | -6.9 | -6.1 |
| -6.2 | -6.0 | -6.2 | -6.4 | -5.9 | -7.0 | -6.7 | -6.2 | -6.2 | -6.6 | -6.4 | -6.4 | -6.5 | -5.9 |
| -6.0 | -5.9 | -6.2 | -6.2 | -5.8 | -7.0 | -6.7 | -6.1 | -5.9 | -6.6 | -6.3 | -6.4 | -6.4 | -5.9 |
| -5.9 | -5.9 | -6.2 | -6.1 | -5.8 | -6.8 | -6.7 | -6.0 | -5.9 | -6.5 | -6.2 | -6.4 | -6.3 | -5.9 |
| -5.8 | -5.9 | -6.0 | -6.0 | -5.8 | -6.8 | -6.6 | -5.9 | -5.8 | -6.5 | -6.1 | -6.3 | -6.2 | -5.9 |
| -5.8 | -5.7 | -6.0 | -6.0 | -5.7 | -6.7 | -6.6 | -5.9 | -5.7 | -6.5 | -6.1 | -6.2 | -6.1 | -5.7 |
| -5.8 | -5.7 | -5.8 | -6.0 | -5.6 | -6.7 | -6.6 | -5.9 | -5.7 | -6.4 | -6.1 | -6.1 | -6.1 | -5.6 |
| -5.8 | -5.7 | -5.9 | -5.8 | -5.6 | -6.6 | -6.6 | -5.9 | -5.7 | -5.8 | -6.0 | -6.1 | -6.0 | -5.6 |

**Table S10.** Scoring values obtained with PLANTS for fisetin per protein-ligand complex of the ensemble

| 3MXF | 3P5O | 3U5L | 4LYW | 4MR4 | 4NUD | 4XYA | 4YH3 | 5KJ0 | 5M3A | 5TI2 | 5TI3 | 5U28 | 5VOM |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| -74.7 | -76.1 | -76.5 | -76.1 | -76.6 | -76.8 | -76.0 | -74.3 | -72.6 | -75.2 | -74.6 | -79.6 | -75.9 | -71.6 |
| -73.7 | -74.5 | -75.3 | -74.9 | -75.4 | -76.3 | -73.4 | -73.0 | -72.3 | -74.2 | -74.2 | -75.2 | -73.9 | -69.8 |
| -71.9 | -73.2 | -73.3 | -72.3 | -73.5 | -74.9 | -72.3 | -71.2 | -70.3 | -73.4 | -73.1 | -74.8 | -70.7 | -68.9 |
| -71.8 | -72.0 | -73.2 | -72.1 | -72.6 | -73.4 | -70.1 | -70.9 | -69.8 | -73.2 | -71.7 | -72.2 | -70.5 | -68.7 |
| -71.7 | -71.8 | -71.6 | -71.4 | -71.6 | -69.3 | -69.9 | -69.9 | -68.9 | -73.0 | -69.0 | -71.6 | -70.4 | -67.1 |
| -69.6 | -70.9 | -69.9 | -68.0 | -71.5 | -68.9 | -69.3 | -69.0 | -68.9 | -71.2 | -68.8 | -71.1 | -69.2 | -66.2 |
| -68.8 | -70.8 | -69.6 | -67.6 | -71.2 | -68.8 | -69.2 | -68.9 | -67.9 | -68.8 | -67.9 | -70.8 | -69.0 | -66.1 |
| -68.0 | -69.2 | -67.2 | -66.7 | -69.8 | -68.6 | -69.0 | -68.9 | -67.0 | -68.7 | -67.5 | -70.0 | -66.4 | -65.9 |
| -67.8 | -68.9 | -67.2 | -66.5 | -69.8 | -68.2 | -68.7 | -66.8 | -66.5 | -68.1 | -67.0 | -69.7 | -66.2 | -65.0 |

**Table S11.** Scoring values obtained with Vina for fisetin per protein-ligand complex of the ensemble

| 3MXF | 3P5O | 3U5L | 4LYW | 4MR4 | 4NUD | 4XYA | 4YH3 | 5KJ0 | 5M3A | 5TI2 | 5TI3 | 5U28 | 5VOM |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| -8.0 | -8.1 | -8.3 | -8.2 | -8.4 | -8.4 | -8.4 | -8.2 | -8.5 | -8.6 | -8.5 | -8.5 | -8.0 | -7.9 |
| -8.0 | -8.1 | -8.3 | -8.0 | -8.1 | -8.3 | -8.3 | -7.9 | -8.5 | -8.6 | -8.1 | -8.5 | -7.8 | -7.7 |
| -8.0 | -8.0 | -8.2 | -7.9 | -8.0 | -8.3 | -8.3 | -7.8 | -8.3 | -8.5 | -8.1 | -8.5 | -7.7 | -7.7 |
| -8.0 | -8.0 | -8.2 | -7.9 | -7.8 | -8.2 | -8.3 | -7.8 | -8.3 | -8.3 | -7.9 | -8.4 | -7.6 | -7.7 |
| -7.9 | -8.0 | -8.1 | -7.9 | -7.7 | -8.2 | -8.2 | -7.7 | -8.1 | -8.3 | -7.8 | -8.2 | -7.5 | -7.6 |
| -7.8 | -7.9 | -8.0 | -7.8 | -7.7 | -8.0 | -8.2 | -7.6 | -8.1 | -8.2 | -7.8 | -8.0 | -7.5 | -7.6 |
| -7.8 | -7.6 | -7.9 | -7.8 | -7.6 | -7.9 | -8.1 | -7.4 | -8.0 | -8.1 | -7.8 | -8.0 | -7.5 | -7.4 |
| -7.7 | -7.6 | -7.8 | -7.8 | -7.6 | -7.7 | -8.1 | -7.4 | -8.0 | -8.1 | -7.7 | -7.9 | -7.5 | -7.4 |
| -7.5 | -7.5 | -7.7 | -7.6 | -7.5 | -7.7 | -8.1 | -7.2 | -8.0 | -8.1 | -7.6 | -7.9 | -7.4 | -7.1 |

**Figure S1.** Relaxation protocol and MD workflow used in this work.

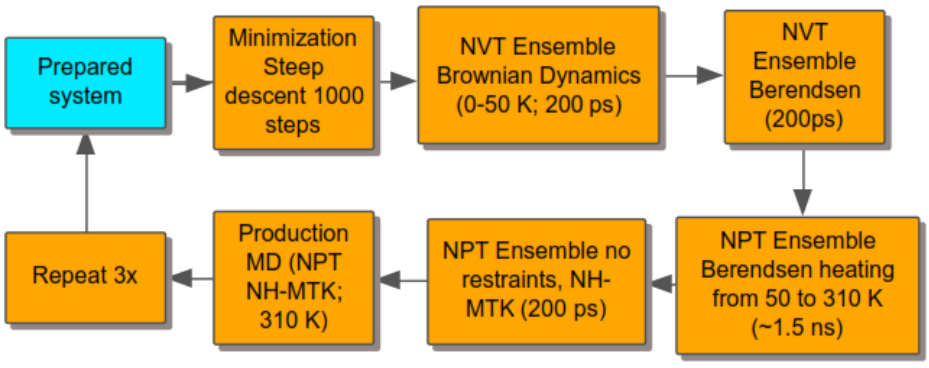

**Figure S2.** Simulation Quality parameters for the BRD4 protein for 100 ns

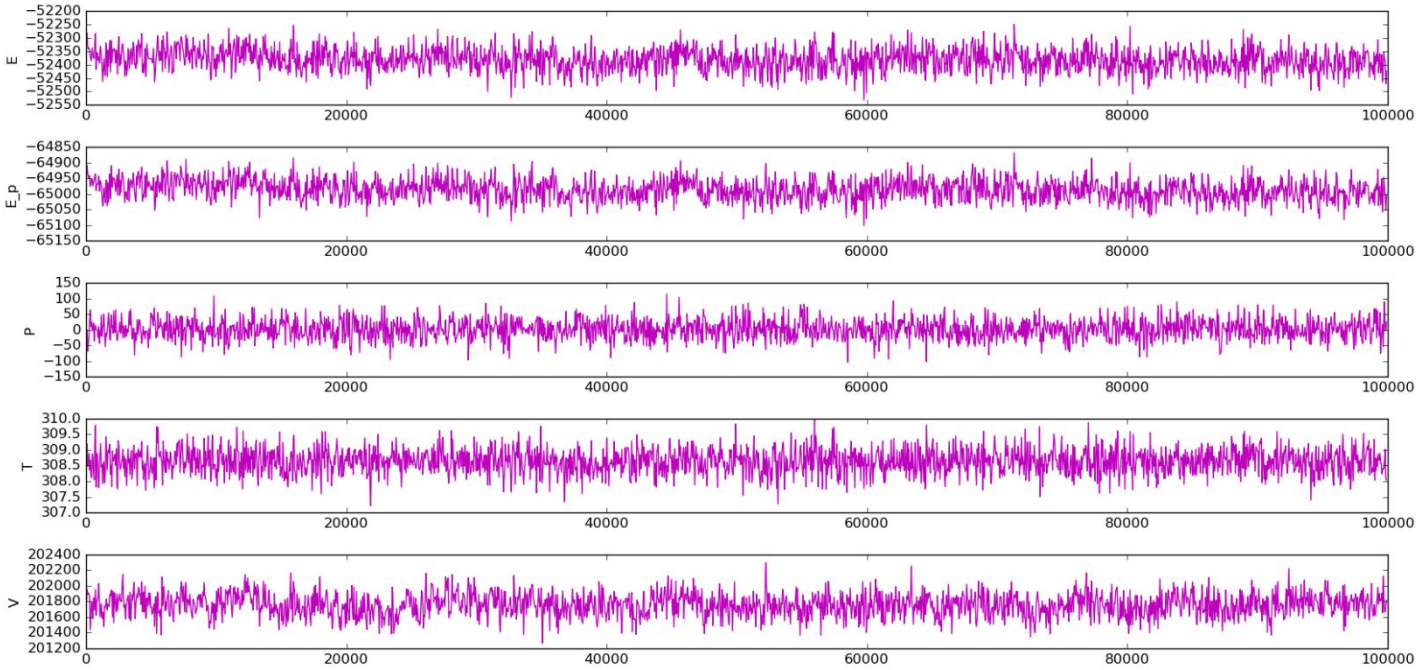


**Table S12.** Summary values for quality measures for the BRD4 protein

| Measure | Average | St. Dev. | Slope ($ps^{-1}$) |
|---|---|---|---|
| Energy (kcal/mol) | **-52381.523** | **43.182** | **0** |
| E_pot (kcal/mol) | **-64986.594** | **34.152** | **0** |
| Temperature (K) | **308.638** | **0.405** | **0** |
| Pressure (bar) | **1.386** | **31.871** | **0** |
| Volume ($Å^3$) | **201756.219** | **148.561** | **0** |

**Figure S3.** RMSD values for BRD4 protein for 100ns

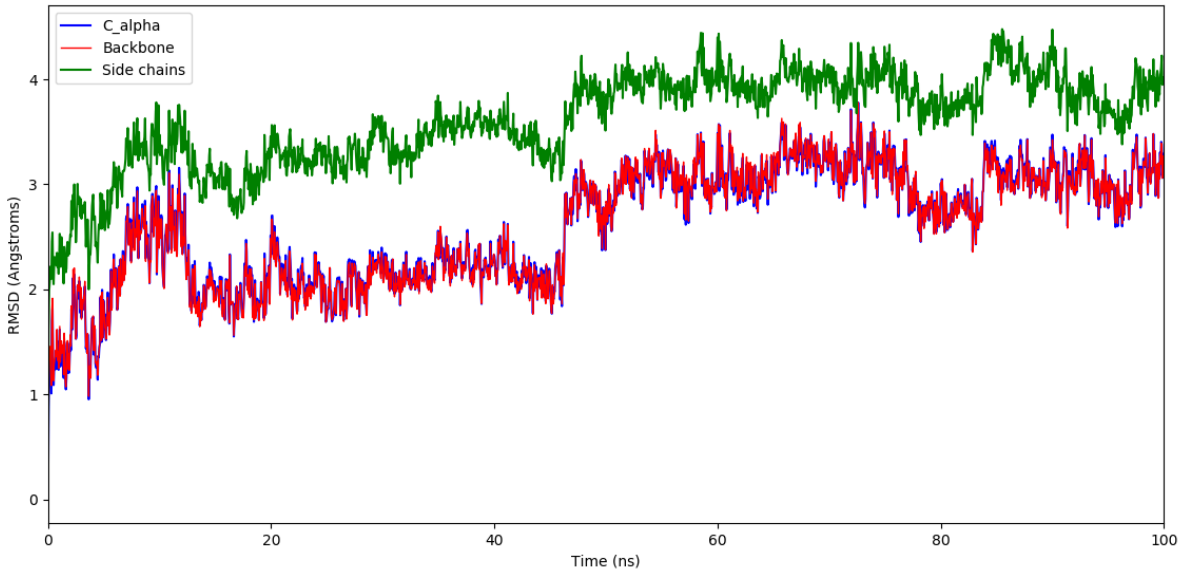

**Figure S4.** Simulation Quality parameters for the BRD4 protein with fisetine for 100 ns

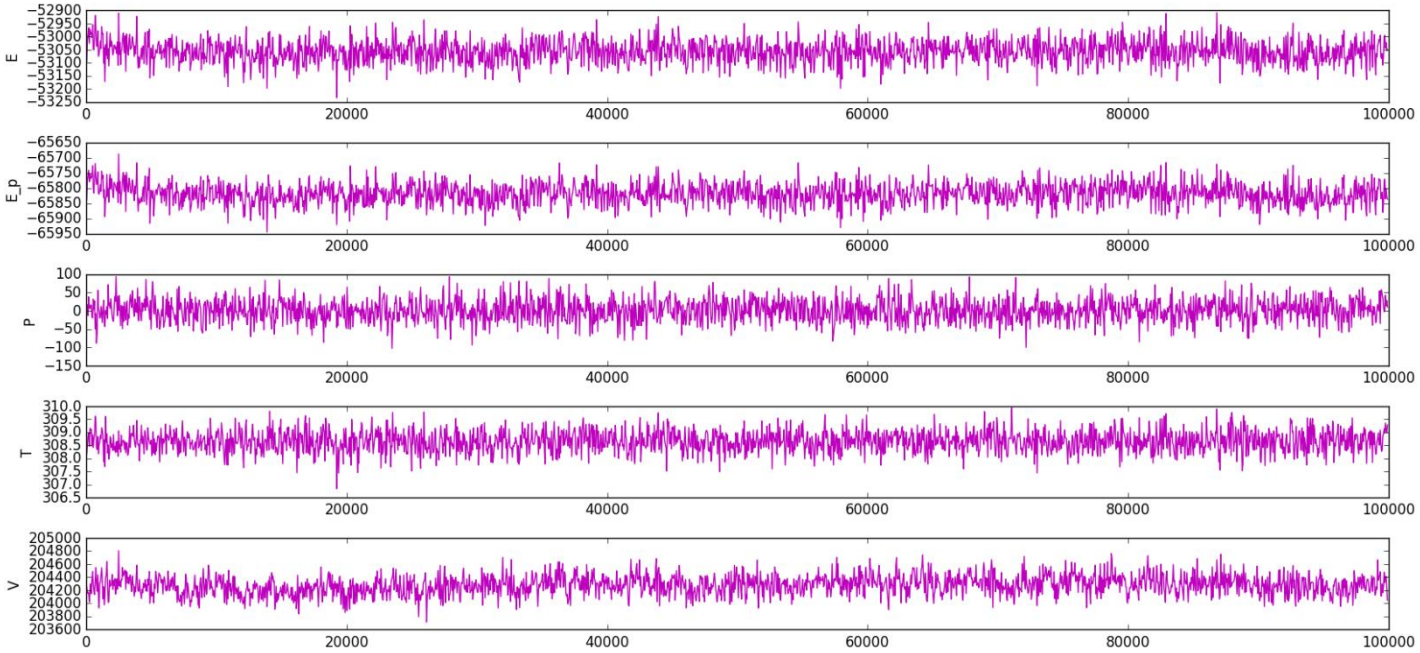


**Table S13.** Summary values for quality measures BRD4 protein with fisetine

| Measure | Average | St. Dev. | Slope ($ps^{-1}$) |
|---|---|---|---|
| Energy (kcal/mol) | **-52181.24** | **44.07** | **0** |
| E_pot (kcal/mol) | **-65818.84** | **34.67** | **0** |
| Temperature (K) | **308.652** | **0.412** | **0** |
| Pressure (bar) | **0.75** | **30.571** | **0** |
| Volume ($Å^3$) | **204276.453** | **151.85** | **0.001** |

**Figure S5.** Simulation Quality parameters for the BRD4 protein with amentoflavone for 100 ns

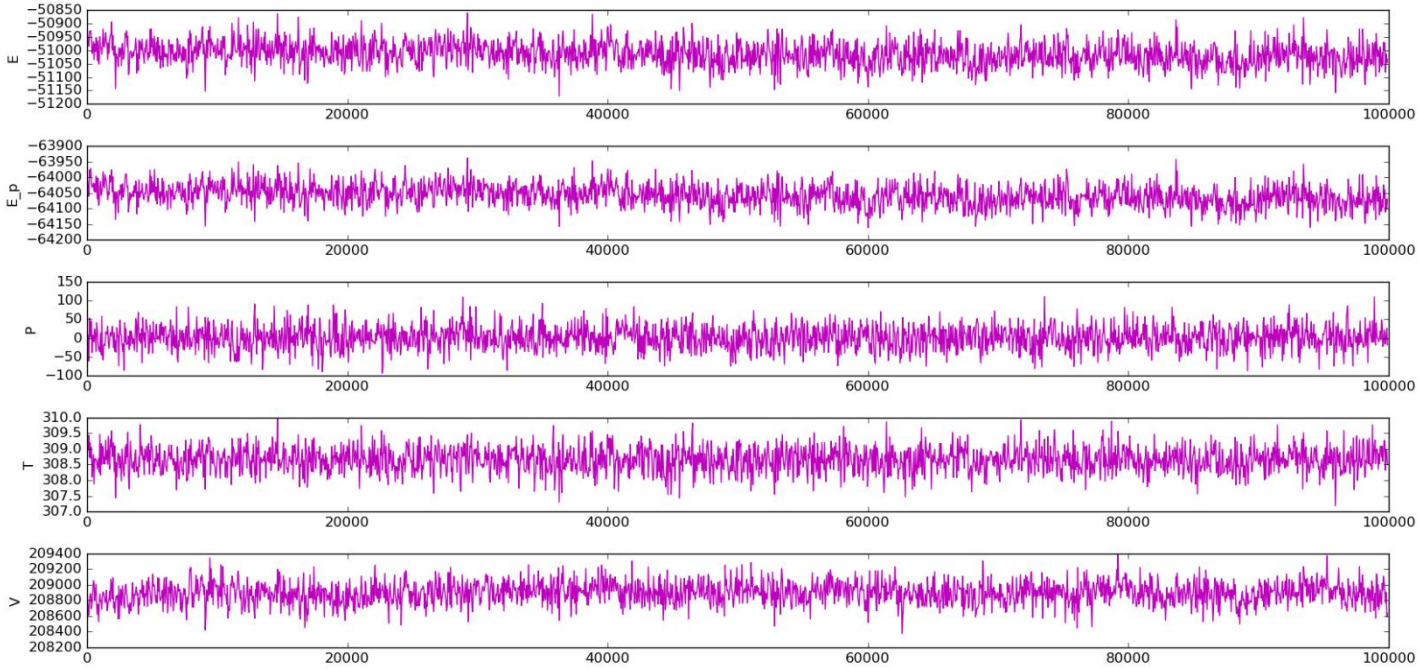

**Table S14.** Summary values for quality measures BRD4 protein with amentoflavone

| Measure | Average | St. Dev. | Slope ($ps^{-1}$) |
|---|---|---|---|
| Energy (kcal/mol) | **-51014.1** | **45.84** | **0** |
| E_pot (kcal/mol) | **-64057.84** | **35.95** | **0** |
| Temperature (K) | **308.655** | **0.4** | **0** |
| Pressure (bar) | **0.946** | **31.592** | **0** |
| Volume ($Å^3$) | **208895.878** | **142.446** | **0** |

**Figure S6.** Secondary structure of BRD4 as observed for 100 ns. A) BRD4 without ligand. B) amentoflavone. C) fisetin