Supporting Information

# Allosteric Binding Sites On Nuclear Receptors: Focus On Drug Efficacy and Selectivity

André Fischer and Martin Smieško*

*Computational Pharmacy Group, Department of Pharmaceutical Sciences, Klingelbergstrasse 50, 4056 Basel*

*Corresponding author contact: martin.smiesko@unibas.ch*

**Abstract:** Nuclear receptors (NRs) are highly relevant drug targets in major indications such as oncologic, metabolic, reproductive and immunologic diseases. However, currently marketed drugs designed towards the orthosteric binding site of NRs often suffer from resistance mechanisms and poor selectivity. The identification of two superficial allosteric sites activation function-2 (AF-2) and binding function-3 (BF-3) as novel drug targets sparked the development of inhibitors, while selectivity concerns due to a high conservation degree remained. To determine important pharmacophores and hydration sites among AF-2 and BF-3 of eight hormonal NRs, we systematically analyzed over 10 µs of molecular dynamics simulations including simulations in explicit water and solvent mixtures. In addition, a library of over 300 allosteric inhibitors was evaluated by molecular docking. Based on our results, we suggest the BF-3 site to offer a higher potential for drug selectivity as opposed to the AF-2 site that is more conserved among the selected receptors. Detected similarities among the AF-2 sites of various NRs urge for a broader selectivity assessment in future studies. In combination with the supporting materials, this work provides a foundation to improve both selectivity and potency of allosteric inhibitors in a rational manner and increase the therapeutic applicability of this promising compound class.

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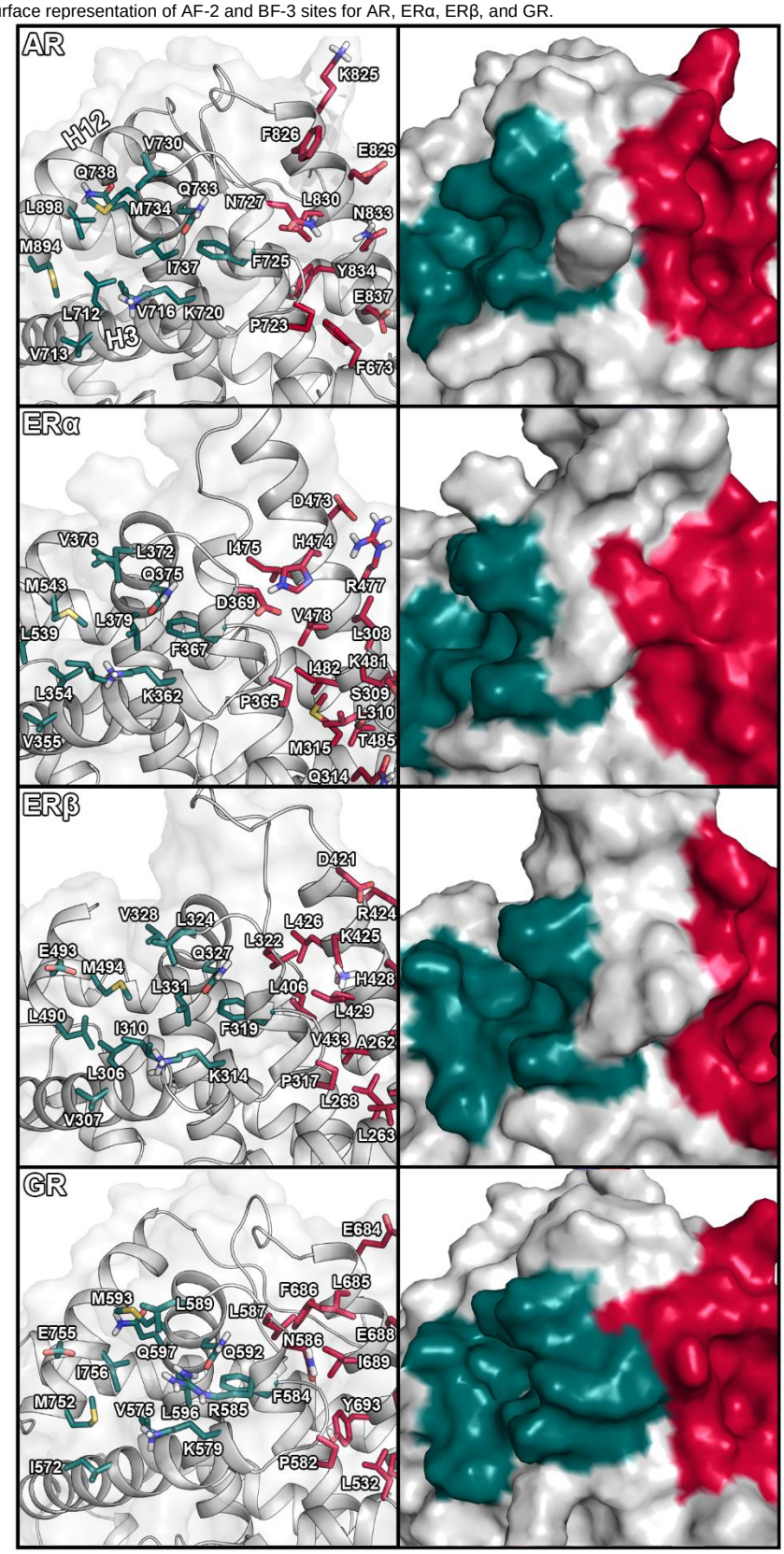
## Supporting Results and Discussion

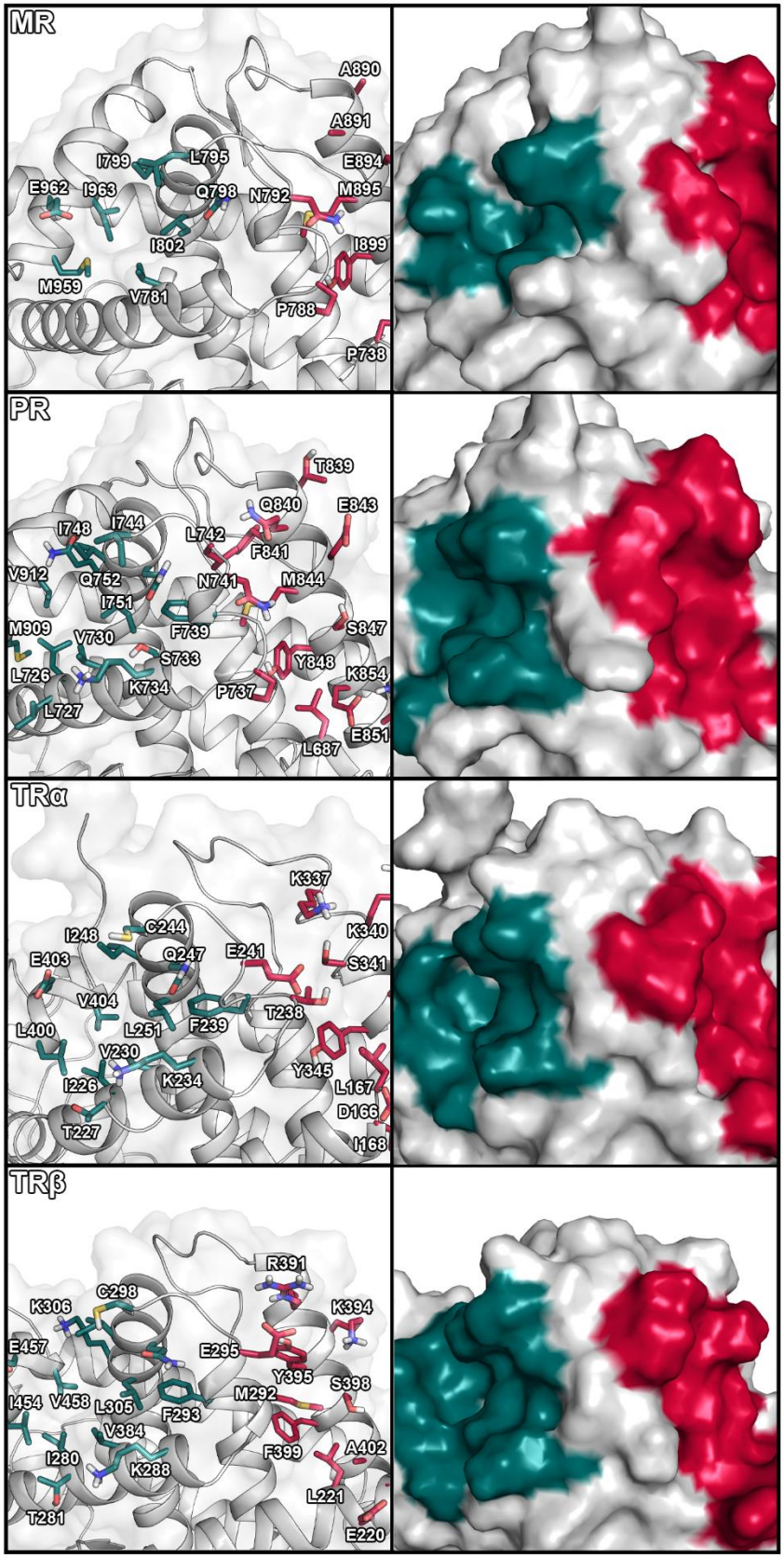
### Sequence Similarity Among Hormonal NRs

**Figure S1**. Residues and surface representation of AF-2 and BF-3 sites for AR, ERα, ERβ, and GR.




Representation of the AF-2 and BF-3 sites of AR, ERα, ERβ, and GR. The AF-2 is shown in pine green, while the BF-3 site was colored red. The surface was colored according to the type of residue (blue, positive charge; red, negative charge; green, non-polar; yellow, cysteine; purple, glycine; light blue, histidine).

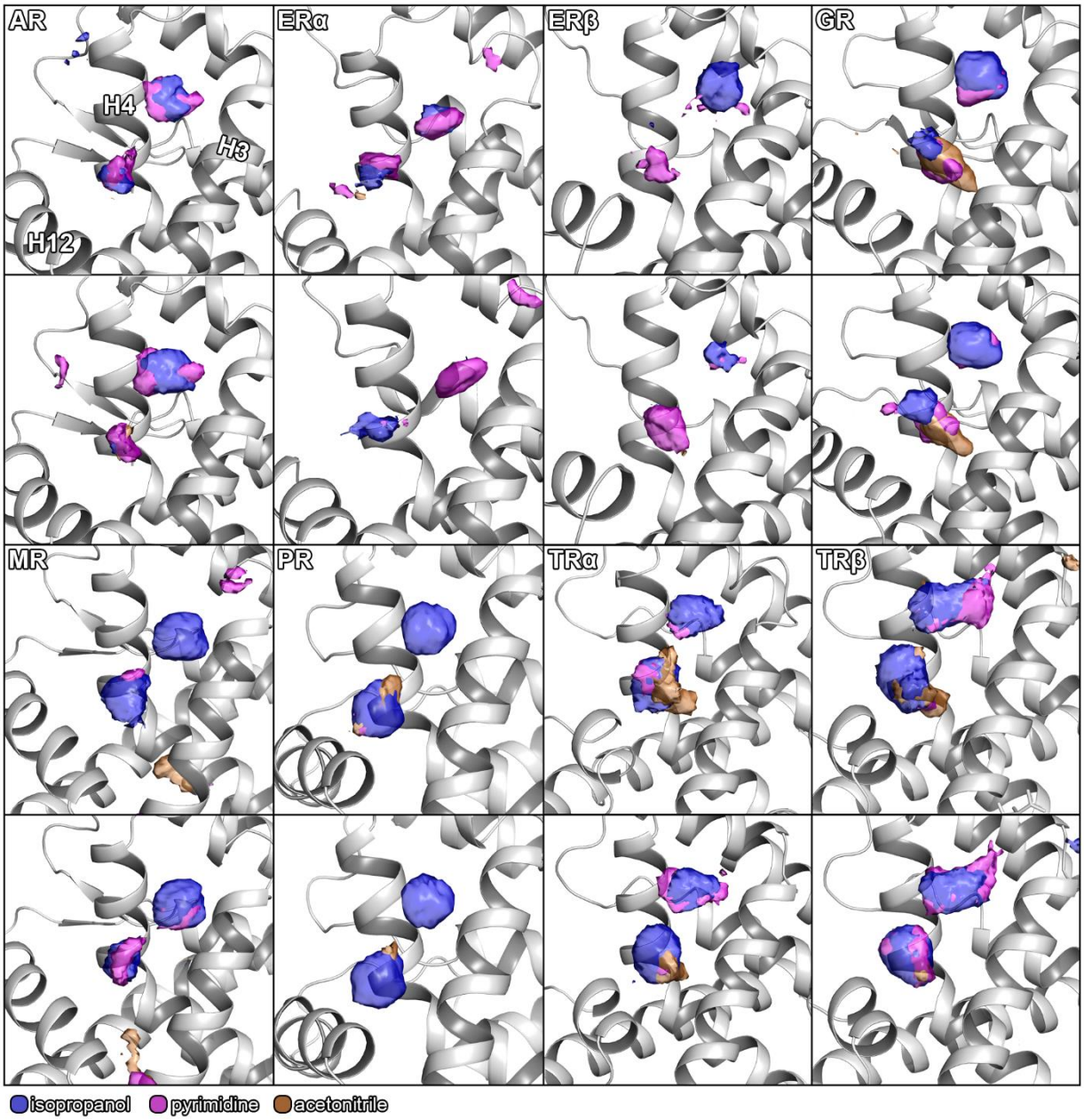
**Figure S2**. Residues and surface representation of AF-2 and BF-3 sites for MR, PR, TRα, and TRβ.




Representation of the AF-2 and BF-3 sites MR, PR, TRα, and TRβ. The AF-2 is shown in pine green, while the BF-3 site was colored red. The surface was colored according to the type of residue (blue, positive charge; red, negative charge; green, non-polar; yellow, cysteine; purple, glycine; light blue, histidine).

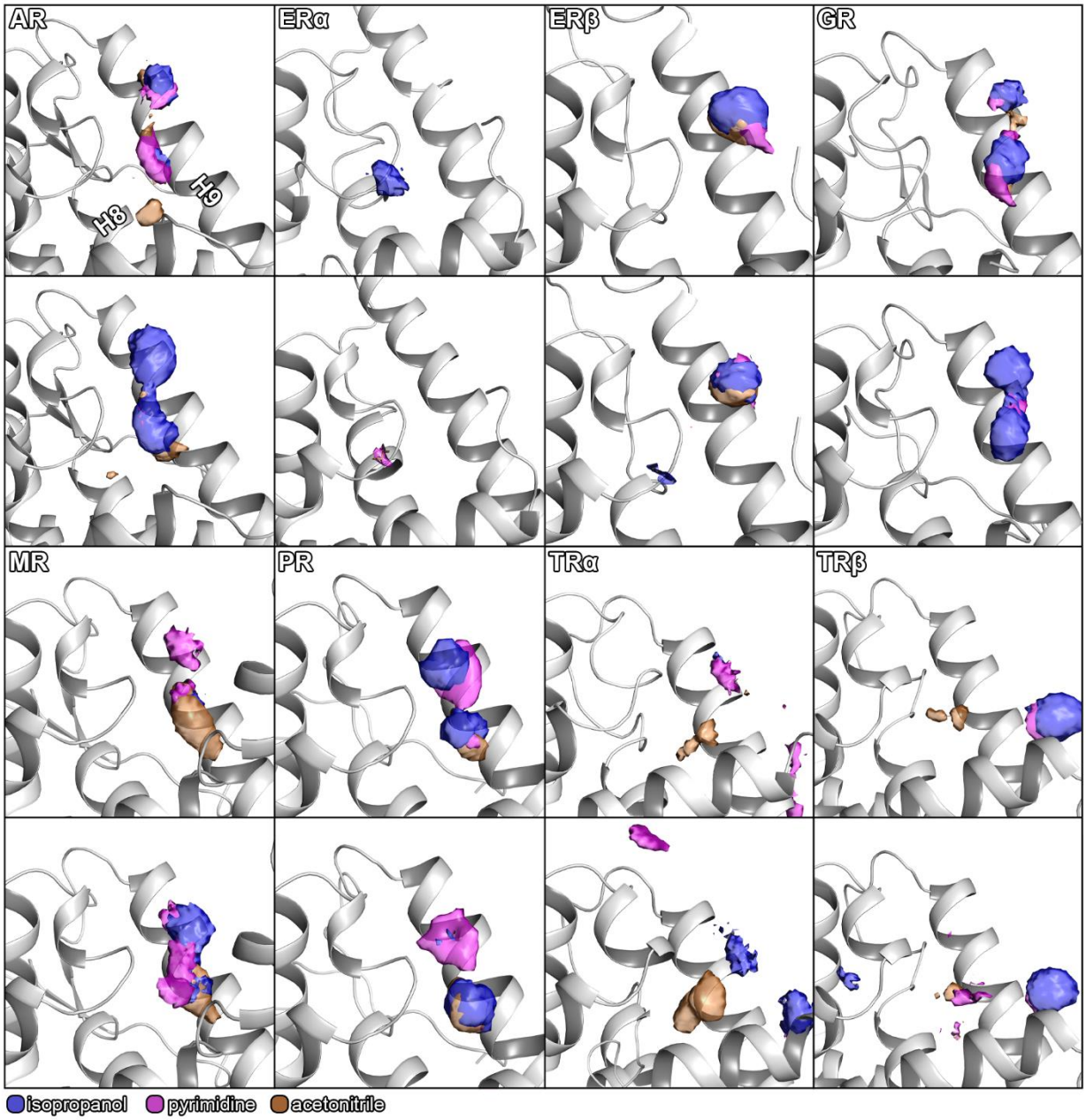
## Distinct Pharmacophores of the Allosteric Sites

**Figure S3**. Comparison between cosolvent densities between apo and holo protein for the AF-2 site.




For each receptor, a comparison of the probe densities between holo (upper part) and apo (lower part) structure is shown. The densities are shown at an isovalue of 12. A legend to interpret the colors is given below the figure. The viewpoint was held consistent.

**Figure S4**. Comparison between cosolvent densities between apo and holo protein for the BF-3 site.




For each receptor, a comparison of the probe densities between holo (upper part) and apo (lower part) structure is shown. The densities are shown at an isovalue of 12. A legend to interpret the colors is given in below the figure. The viewpoint was held consistent.

**Table S1.** Backbone RMSD of AR cosolvent MD simulations.

| Replica | Acetonitrile apo | Isopropanol apo | Pyrimidine apo | Acetonitrile holo | Isopropanol holo | Pyrimidine holo |
|---|---|---|---|---|---|---|
| 1 | 1.30 | 1.20 | 1.59 | 1.14 | 1.27 | 1.10 |
| 2 | 1.24 | 1.33 | 1.46 | 1.13 | 1.07 | 1.24 |
| 3 | 1.51 | 1.37 | 1.66 | 1.08 | 1.29 | 1.23 |
| 4 | 1.44 | 1.34 | 1.44 | 1.16 | 1.26 | 1.36 |
| 5 | 1.33 | 1.50 | 1.67 | 1.06 | 1.40 | 1.22 |
| 6 | 1.47 | 1.12 | 1.56 | 1.15 | 1.22 | 1.27 |
| 7 | 1.55 | 1.39 | 1.80 | 1.08 | 1.07 | 1.10 |
| 8 | 1.45 | 1.14 | 1.07 | 1.23 | 1.25 | 1.19 |
| 9 | 1.40 | 1.42 | 1.37 | 0.97 | 1.31 | 1.13 |
| 10 | 1.46 | 1.33 | 1.36 | 1.49 | 1.25 | 1.29 |

The backbone RMSD (Å) was determined between the input structure of the simulations and the last frame of the respective replica.

**Table S2.** Backbone RMSD of ERα cosolvent MD simulations.

| Replica | Acetonitrile apo | Isopropanol apo | Pyrimidine apo | Acetonitrile holo | Isopropanol holo | Pyrimidine holo |
|---|---|---|---|---|---|---|
| 1 | 1.71 | 1.37 | 1.26 | 1.44 | 1.36 | 1.53 |
| 2 | 1.51 | 2.13 | 1.37 | 1.40 | 1.47 | 1.20 |
| 3 | 1.24 | 1.71 | 1.29 | 1.81 | 1.25 | 1.32 |
| 4 | 1.14 | 1.24 | 1.46 | 1.47 | 1.43 | 1.85 |
| 5 | 1.53 | 1.22 | 1.45 | 1.42 | 1.71 | 1.55 |
| 6 | 1.54 | 1.43 | 1.22 | 1.44 | 1.50 | 1.35 |
| 7 | 1.56 | 1.77 | 1.49 | 1.66 | 1.24 | 1.57 |
| 8 | 1.36 | 1.89 | 1.37 | 1.36 | 1.07 | 1.81 |
| 9 | 1.38 | 1.42 | 1.46 | 1.04 | 1.50 | 1.37 |
| 10 | 1.92 | 1.34 | 1.65 | 1.31 | 1.19 | 1.65 |

The RMSD (Å) was determined between the input structure of the simulations and the last frame of the respective replica.

**Table S3.** Backbone RMSD of ERβ cosolvent MD simulations.

| Replica | Acetonitrile apo | Isopropanol apo | Pyrimidine apo | Acetonitrile holo | Isopropanol holo | Pyrimidine holo |
|---|---|---|---|---|---|---|
| 1 | 2.19 | 1.61 | 1.88 | 1.36 | 1.48 | 1.48 |
| 2 | 1.60 | 1.59 | 1.29 | 1.24 | 1.35 | 1.67 |
| 3 | 1.90 | 1.54 | 1.74 | 1.81 | 1.27 | 1.59 |
| 4 | 1.55 | 1.74 | 1.68 | 1.59 | 1.28 | 1.48 |
| 5 | 1.75 | 1.87 | 2.01 | 1.39 | 1.55 | 1.45 |
| 6 | 1.88 | 1.36 | 1.99 | 1.45 | 1.22 | 1.28 |
| 7 | 1.45 | 1.79 | 1.56 | 1.27 | 1.81 | 1.48 |
| 8 | 1.74 | 1.54 | 1.43 | 1.44 | 1.65 | 1.40 |
| 9 | 1.44 | 1.67 | 1.87 | 1.64 | 1.22 | 1.42 |
| 10 | 1.88 | 1.51 | 1.89 | 1.40 | 1.19 | 1.74 |

The RMSD (Å) was determined between the input structure of the simulations and the last frame of the respective replica.

**Table S4.** Backbone RMSD of GR cosolvent MD simulations.

| Replica | Acetonitrile apo | Isopropanol apo | Pyrimidine apo | Acetonitrile holo | Isopropanol holo | Pyrimidine holo |
|---|---|---|---|---|---|---|
| 1 | 1.30 | 1.43 | 1.14 | 1.30 | 1.40 | 1.29 |
| 2 | 1.33 | 1.36 | 1.14 | 1.04 | 1.28 | 1.35 |
| 3 | 1.29 | 1.38 | 1.07 | 1.17 | 1.42 | 1.36 |
| 4 | 1.27 | 1.16 | 1.10 | 1.22 | 1.18 | 1.14 |
| 5 | 1.38 | 1.29 | 1.39 | 1.15 | 1.26 | 1.20 |
| 6 | 1.26 | 1.42 | 1.21 | 1.23 | 1.16 | 1.19 |
| 7 | 1.24 | 1.14 | 1.24 | 1.15 | 1.24 | 1.07 |
| 8 | 1.24 | 1.51 | 1.39 | 1.23 | 1.08 | 1.36 |
| 9 | 1.27 | 1.41 | 1.35 | 1.25 | 1.23 | 1.25 |
| 10 | 1.36 | 1.22 | 1.14 | 1.33 | 1.08 | 1.29 |

The backbone RMSD (Å) was determined between the input structure of the simulations and the last frame of the respective replica.

**Table S5.** Backbone RMSD of MR cosolvent MD simulations.

| Replica | Acetonitrile apo | Isopropanol apo | Pyrimidine apo | Acetonitrile holo | Isopropanol holo | Pyrimidine holo |
|---|---|---|---|---|---|---|
| 1 | 1.31 | 1.44 | 1.86 | 1.61 | 1.60 | 1.46 |
| 2 | 1.56 | 1.30 | 1.47 | 1.69 | 1.30 | 1.78 |
| 3 | 1.68 | 1.76 | 1.73 | 1.41 | 1.51 | 1.50 |
| 4 | 1.78 | 1.68 | 1.88 | 1.38 | 1.50 | 1.37 |
| 5 | 1.67 | 1.48 | 1.74 | 1.48 | 1.59 | 1.49 |
| 6 | 1.61 | 1.69 | 1.53 | 1.67 | 1.58 | 1.33 |
| 7 | 1.41 | 1.40 | 1.84 | 1.35 | 1.48 | 1.78 |
| 8 | 1.39 | 1.54 | 1.59 | 1.49 | 1.45 | 1.40 |
| 9 | 1.42 | 1.43 | 1.66 | 1.72 | 1.59 | 1.56 |
| 10 | 1.25 | 1.87 | 1.70 | 1.68 | 1.28 | 1.36 |

The backbone RMSD (Å) was determined between the input structure of the simulations and the last frame of the respective replica.

**Table S6.** Backbone RMSD of PR cosolvent MD simulations.

| Replica | Acetonitrile apo | Isopropanol apo | Pyrimidine apo | Acetonitrile holo | Isopropanol holo | Pyrimidine holo |
|---|---|---|---|---|---|---|
| 1 | 1.29 | 1.10 | 1.18 | 1.10 | 0.87 | 1.19 |
| 2 | 1.12 | 1.05 | 1.04 | 0.98 | 0.81 | 1.28 |
| 3 | 0.98 | 1.26 | 1.06 | 1.07 | 1.04 | 0.91 |
| 4 | 1.03 | 0.97 | 1.21 | 1.00 | 1.06 | 0.90 |
| 5 | 1.07 | 0.89 | 1.17 | 1.17 | 1.02 | 1.09 |
| 6 | 1.04 | 1.41 | 1.02 | 1.12 | 1.29 | 1.03 |
| 7 | 1.14 | 1.14 | 1.23 | 1.05 | 1.40 | 1.30 |
| 8 | 1.07 | 1.23 | 1.06 | 1.05 | 1.05 | 1.03 |
| 9 | 1.18 | 0.91 | 1.26 | 0.98 | 1.02 | 1.27 |
| 10 | 1.16 | 1.13 | 1.14 | 1.05 | 1.07 | 1.12 |

The backbone RMSD (Å) was determined between the input structure of the simulations and the last frame of the respective replica.

**Table S7.** Backbone RMSD of TRα cosolvent MD simulations.

| Replica | Acetonitrile apo | Isopropanol apo | Pyrimidine apo | Acetonitrile holo | Isopropanol holo | Pyrimidine holo |
|---|---|---|---|---|---|---|
| 1 | 2.15 | 1.82 | 1.96 | 1.84 | 1.67 | 2.41 |
| 2 | 1.85 | 1.45 | 1.75 | 1.97 | 2.02 | 1.24 |
| 3 | 1.86 | 1.30 | 1.64 | 2.03 | 2.28 | 2.01 |
| 4 | 1.64 | 2.12 | 1.90 | 1.60 | 1.32 | 1.51 |
| 5 | 1.94 | 2.57 | 1.56 | 1.69 | 2.35 | 2.23 |
| 6 | 2.37 | 1.91 | 1.86 | 2.44 | 1.69 | 2.11 |
| 7 | 2.03 | 1.76 | 2.25 | 1.97 | 1.61 | 1.82 |
| 8 | 1.74 | 2.01 | 2.21 | 1.82 | 1.93 | 1.72 |
| 9 | 1.71 | 1.73 | 1.93 | 1.91 | 2.32 | 1.82 |
| 10 | 2.03 | 1.85 | 1.63 | 1.88 | 1.92 | 2.08 |

The backbone RMSD (Å) was determined between the input structure of the simulations and the last frame of the respective replica.

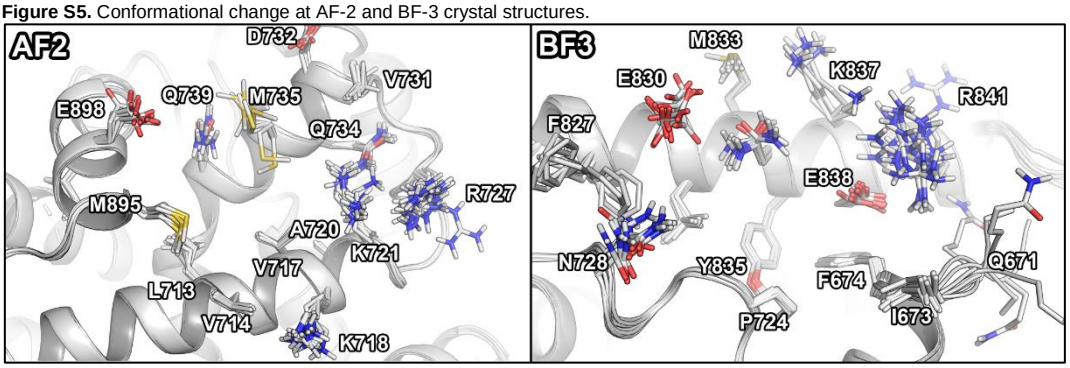
**Table S8.** Backbone RMSD of TRβ cosolvent MD simulations.

| Replica | Acetonitrile apo | Isopropanol apo | Pyrimidine apo | Acetonitrile holo | Isopropanol holo | Pyrimidine holo |
|---|---|---|---|---|---|---|
| 1 | 1.51 | 1.49 | 1.38 | 1.51 | 1.85 | 1.95 |
| 2 | 1.42 | 1.77 | 1.75 | 1.55 | 1.40 | 1.64 |
| 3 | 1.56 | 1.72 | 1.51 | 1.54 | 1.55 | 1.69 |
| 4 | 1.64 | 1.24 | 1.32 | 1.51 | 1.51 | 1.68 |
| 5 | 1.87 | 1.61 | 1.73 | 1.55 | 1.69 | 1.91 |
| 6 | 1.58 | 1.90 | 1.50 | 1.71 | 1.70 | 1.61 |
| 7 | 1.48 | 1.65 | 1.32 | 1.55 | 1.31 | 1.74 |
| 8 | 1.63 | 1.62 | 1.43 | 1.56 | 1.65 | 1.59 |
| 9 | 1.48 | 1.40 | 1.73 | 1.65 | 1.66 | 1.60 |
| 10 | 1.63 | 1.74 | 1.73 | 1.59 | 1.51 | 1.31 |

The backbone RMSD (Å) was determined between the input structure of the simulations and the last frame of the respective replica.

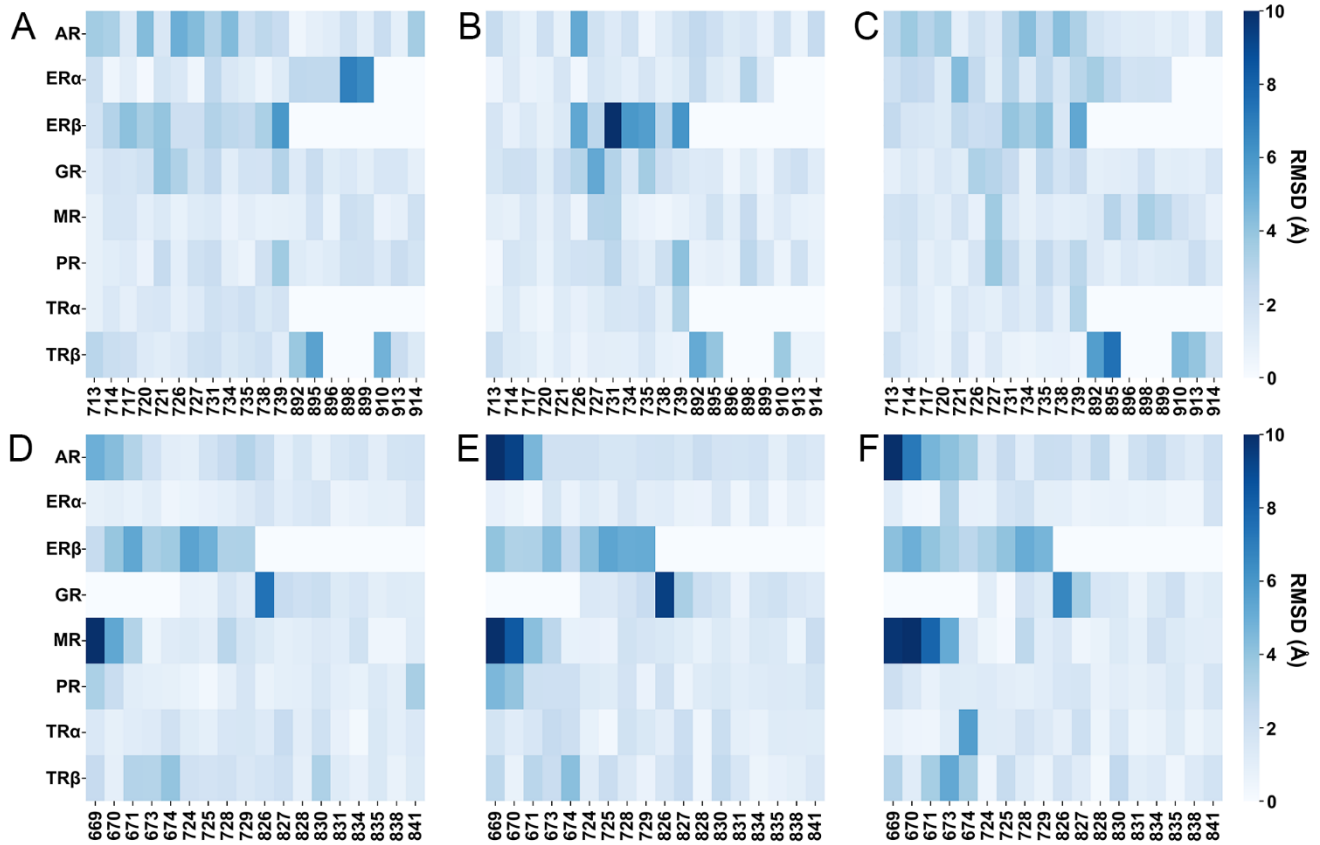
## Conformational Change

**Figure S5.** Conformational change at AF-2 and BF-3 crystal structures.



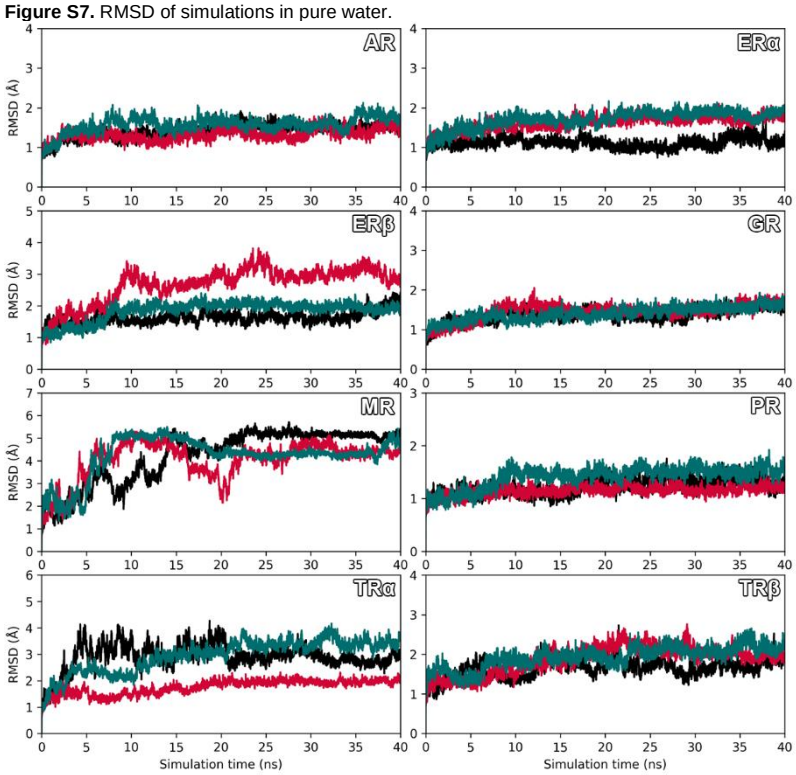

Superposition of holo crystal structures of the allosteric site (PDB IDs: 2PIP, 2PIV, 2YHD, 2YLO, 2YLP, 2PIT, 2PIU, 2PIO, 2PKL, 2YLQ, 2PIW, 4HLW)

**Figure S6.** Conformational change at AF-2 and BF-3 determined by RMSD.




The RMSD between the representative structures of cosolvent and pure water simulations is shown for (A) AF-2 site in acetonitrile, (B) AF-2 in isopropanol, (B) AF-2 in pyrimidine, (D) BF-3 in acetonitrile, (E) BF-3 in isopropanol, and (F) BF-3 in pyrimidine.

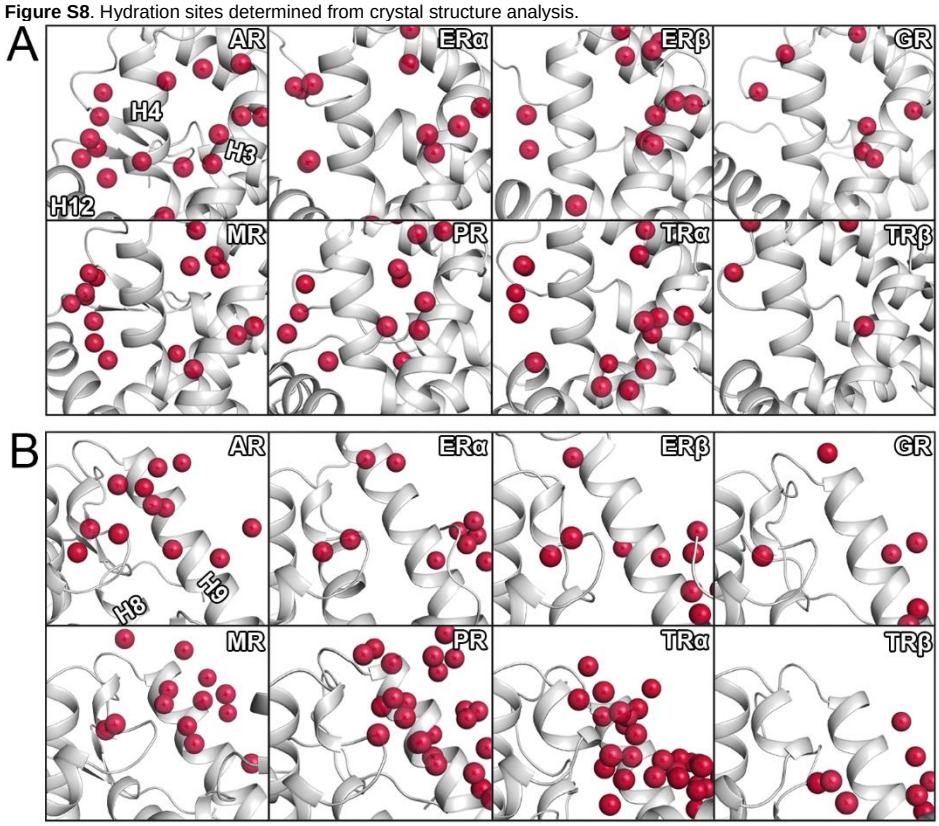
**Figure S7.** RMSD of simulations in pure water.




The backbone RMSD of simulations in pure water (performed in triplicates) is presented for each receptor.

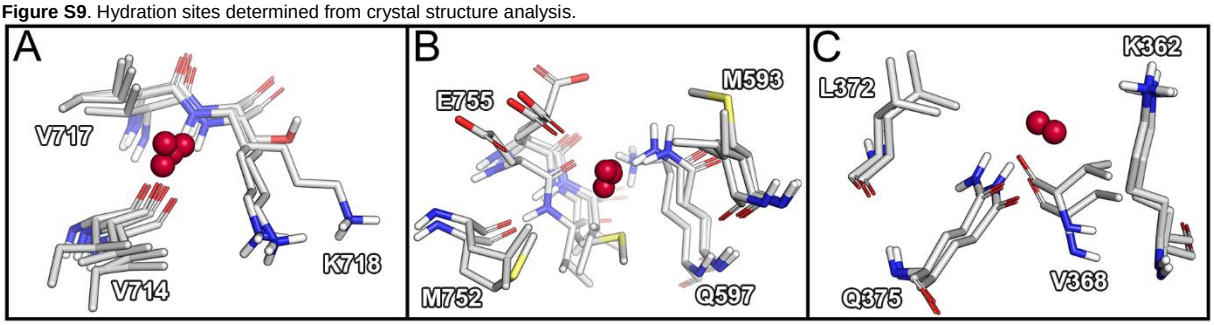
## Hydration Sites of the Allosteric Sites

**Figure S8**. Hydration sites determined from crystal structure analysis.



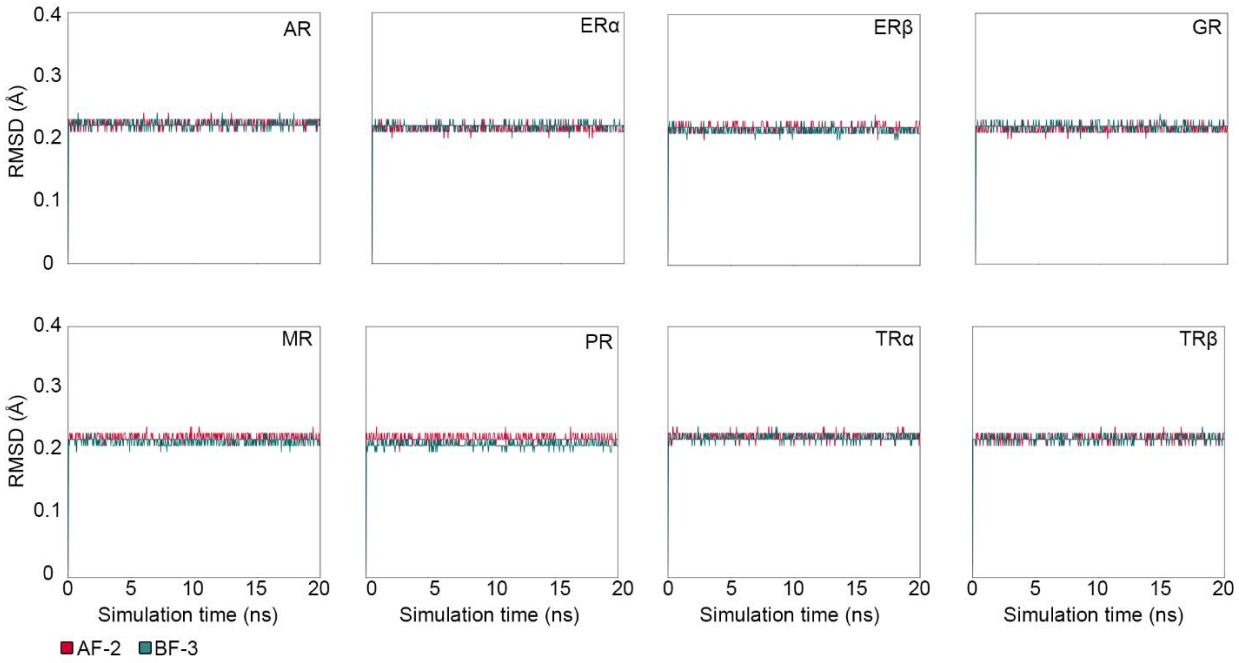

The hydration sites determined to be conserved in the hydration site analysis based on crystal structures. While (A) highlights the AF-2 site the (B) panel presents the BF-3 site.

**Figure S9**. Hydration sites determined from crystal structure analysis.




(A) Hydration site conserved among AR, ERβ, GR and MR. (B) Hydration site conserved among ERβ, GR, PR, TRβ. (C) Hydration site conserved among ERs. The nomenclature for the shown residues was selected based on (A) AR, (B) GR, and (C) ERα.

**Figure S10**. RMSD analysis of WATsite simulations.




The backbone RMSD of WATsite simulations is presented for each receptor. Since a separate simulation was performed for each site, different colors were used to indicate the respective simulation.

**Table S9.** Results from the hydration site analysis using WATsite for the AR.

| Site | Hydration site | Enthalpy ΔH (kcal/mol) | Entropy -T*ΔS (kcal/mol) |
|---|---|---|---|
| AF-2 | 1 | -0.494 | 1.242 |
| | 2 | -1.776 | 2.283 |
| | 3 | -0.804 | 1.546 |
| | 4 | 3.317 | 1.039 |
| | 5 | 0.396 | 1.891 |
| | 6 | -1.051 | 1.247 |
| | 7 | 0.697 | 1.242 |
| | 8 | 1.938 | 1.232 |
| | 9 | 3.129 | 1.951 |
| | 10 | 0.762 | 1.037 |
| | 11 | 0.397 | 1.134 |
| | 12 | 2.685 | 1.514 |
| | 13 | 0.876 | 1.022 |
| | 14 | -0.157 | 1.138 |
| | 15 | -0.306 | 1.338 |
| | 16 | 1.105 | 1.280 |
| | 17 | -1.167 | 1.799 |
| | 18 | 1.060 | 1.985 |
| | 19 | 0.663 | 1.237 |
| | 20 | 2.341 | 2.256 |
| | 21 | 4.476 | 1.851 |
| BF-3 | 1 | -0.034 | 1.078 |
| | 2 | 0.027 | 1.205 |
| | 3 | 4.036 | 1.393 |
| | 4 | 0.442 | 1.251 |
| | 5 | -3.028 | 1.323 |
| | 6 | 1.624 | 2.949 |
| | 7 | -0.946 | 1.510 |
| | 8 | 0.378 | 0.826 |
| | 9 | -2.587 | 1.394 |
| | 10 | -3.142 | 1.758 |
| | 11 | -0.358 | 2.578 |
| | 12 | -1.936 | 1.841 |
| | 13 | -2.465 | 1.193 |
| | 14 | 1.714 | 0.810 |
| | 15 | -2.561 | 1.347 |
| | 16 | -0.541 | 2.307 |
| | 17 | 2.653 | 1.143 |
| | 18 | -2.133 | 1.276 |
| | 19 | 0.986 | 1.018 |
| | 20 | -2.732 | 1.921 |
| | 21 | -0.579 | 1.131 |
| | 22 | -0.993 | 1.486 |
| | 23 | -2.741 | 1.400 |
| | 24 | -2.128 | 2.719 |
| | 25 | 0.412 | 1.001 |
| | 26 | 0.797 | 1.657 |
| | 27 | -0.446 | 1.274 |
| | 28 | -0.109 | 1.390 |
| | 29 | -0.617 | 1.506 |
| | 30 | -0.832 | 1.838 |
| | 31 | -1.135 | 1.839 |
| | 32 | 0.256 | 1.996 |

Together with supplied PDB files, the contributions for displaced water molecules can be determined.

**Table S10.** Results from the hydration site analysis using WATsite for the ERα.

| Site | Hydration site | Enthalpy ΔH (kcal/mol) | Entropy -T*ΔS (kcal/mol) |
|---|---|---|---|
| AF-2 | 1 | 1.686 | 1.337 |
| | 2 | -0.022 | 1.843 |
| | 3 | -1.204 | 2.276 |
| | 4 | -0.949 | 1.092 |
| | 5 | 1.875 | 1.729 |
| | 6 | -0.098 | 1.159 |
| | 7 | -0.687 | 1.509 |
| | 8 | 1.390 | 1.083 |
| | 9 | 0.784 | 1.085 |
| | 10 | 0.157 | 2.056 |
| | 11 | -0.061 | 1.277 |
| | 12 | 2.390 | 1.538 |
| | 13 | 1.456 | 1.500 |
| | 14 | -0.260 | 1.812 |
| | 15 | 6.644 | 3.013 |
| | 16 | -0.039 | 1.398 |
| BF-3 | 1 | 5.677 | 1.466 |
| | 2 | -1.973 | 1.978 |
| | 3 | 0.662 | 1.664 |
| | 4 | 1.298 | 1.559 |
| | 5 | -4.308 | 2.762 |
| | 6 | 1.416 | 1.238 |
| | 7 | -3.094 | 2.316 |
| | 8 | 0.428 | 0.876 |
| | 9 | -1.836 | 1.438 |
| | 10 | -1.805 | 1.362 |
| | 11 | 1.097 | 2.862 |
| | 12 | -0.945 | 2.275 |
| | 13 | -2.299 | 2.269 |
| | 14 | -2.839 | 3.310 |
| | 15 | -3.174 | 1.960 |
| | 16 | -1.077 | 1.421 |
| | 17 | -0.528 | 1.391 |
| | 18 | -1.890 | 1.626 |
| | 19 | 0.536 | 1.206 |
| | 20 | -3.071 | 1.938 |
| | 21 | 0.640 | 1.240 |
| | 22 | 9.328 | 2.345 |
| | 23 | -2.368 | 2.278 |

Together with supplied PDB files, the contributions for displaced water molecules can be determined.

**Table S11.** Results from the hydration site analysis using WATsite for the ERβ.

| Site | Hydration site | Enthalpy ΔH (kcal/mol) | Entropy -T*ΔS (kcal/mol) |
|---|---|---|---|
| AF-2 | 1 | -2.528 | 1.464 |
| | 2 | 0.318 | 1.260 |
| | 3 | 1.129 | 1.437 |
| | 4 | -0.920 | 1.619 |
| | 5 | 1.322 | 2.024 |
| | 6 | -0.514 | 1.446 |
| | 7 | -1.732 | 1.462 |
| | 8 | 0.288 | 1.003 |
| | 9 | -0.073 | 1.051 |
| | 10 | -0.694 | 1.898 |
| | 11 | -1.062 | 0.897 |
| | 12 | -2.424 | 1.266 |
| | 13 | -0.589 | 1.416 |
| | 14 | 3.443 | 1.117 |
| | 15 | 1.127 | 1.003 |
| | 16 | 3.085 | 3.519 |
| | 17 | 0.101 | 1.432 |
| | 18 | 0.103 | 0.995 |
| | 19 | 0.350 | 1.618 |
| | 20 | 0.650 | 1.423 |
| | 21 | 0.827 | 1.379 |
| | 22 | -0.044 | 1.358 |
| | 23 | -3.236 | 2.227 |
| | 24 | -0.219 | 1.386 |
| | 25 | -0.984 | 2.146 |
| BF-3 | 1 | 0.115 | 1.357 |
| | 2 | -1.174 | 1.054 |
| | 3 | -0.095 | 1.834 |
| | 4 | 0.166 | 1.373 |
| | 5 | -3.478 | 1.714 |
| | 6 | 1.053 | 1.285 |
| | 7 | 3.743 | 1.162 |
| | 8 | 0.872 | 1.109 |
| | 9 | 1.778 | 2.816 |
| | 10 | -3.028 | 1.879 |
| | 11 | -3.195 | 2.644 |
| | 12 | 0.454 | 1.252 |
| | 13 | -1.191 | 1.018 |
| | 14 | -0.243 | 1.976 |
| | 15 | 0.480 | 0.666 |
| | 16 | 0.195 | 1.209 |
| | 17 | -0.939 | 2.012 |
| | 18 | 0.823 | 1.018 |
| | 19 | -3.589 | 2.081 |
| | 20 | 0.613 | 1.636 |
| | 21 | -0.801 | 1.331 |
| | 22 | -0.057 | 2.372 |
| | 23 | -0.722 | 1.071 |
| | 24 | 1.203 | 1.869 |
| | 25 | -0.719 | 1.355 |
| | 26 | 2.975 | 1.397 |
| | 27 | -0.567 | 1.330 |
| | 28 | -0.931 | 1.477 |
| | 29 | -4.742 | 3.268 |
| | 30 | -0.823 | 1.087 |
| | 31 | 2.564 | 1.403 |
| | 32 | 0.435 | 1.403 |
| | 33 | -0.368 | 1.414 |

Together with supplied PDB files, the contributions for displaced water molecules can be determined.

**Table S12.** Results from the hydration site analysis using WATsite for the GR.

| Site | Hydration site | Enthalpy ΔH (kcal/mol) | Entropy -T*ΔS (kcal/mol) |
|---|---|---|---|
| AF-2 | 1 | -1.450 | 1.888 |
| | 2 | 0.020 | 1.125 |
| | 3 | -3.132 | 2.182 |
| | 4 | 0.835 | 1.778 |
| | 5 | -1.745 | 1.478 |
| | 6 | -1.440 | 2.450 |
| | 7 | -0.312 | 1.337 |
| | 8 | -0.371 | 1.123 |
| | 9 | 2.096 | 2.127 |
| | 10 | 3.194 | 2.106 |
| | 11 | -0.748 | 1.273 |
| | 12 | 4.567 | 1.494 |
| | 13 | 0.982 | 1.704 |
| | 14 | 0.454 | 0.994 |
| | 15 | 0.672 | 1.501 |
| | 16 | 0.742 | 1.443 |
| | 17 | -0.151 | 0.982 |
| | 18 | -0.179 | 1.510 |
| | 19 | -0.635 | 1.819 |
| | 20 | 1.841 | 1.301 |
| | 21 | 2.310 | 1.707 |
| | 22 | 3.269 | 1.373 |
| | 23 | -2.419 | 1.809 |
| | 24 | 2.854 | 1.584 |
| | 25 | 1.190 | 1.660 |
| | 26 | -0.165 | 1.510 |
| | 27 | 1.481 | 1.668 |
| | 28 | 1.431 | 1.546 |
| BF-3 | 1 | -1.712 | 2.325 |
| | 2 | -2.350 | 1.518 |
| | 3 | 3.088 | 1.496 |
| | 4 | -2.556 | 1.360 |
| | 5 | -3.629 | 1.710 |
| | 6 | -0.872 | 0.893 |
| | 7 | -2.010 | 1.060 |
| | 8 | 1.369 | 0.979 |
| | 9 | -2.627 | 1.800 |
| | 10 | -2.046 | 1.477 |
| | 11 | -0.318 | 2.084 |
| | 12 | 0.397 | 1.272 |
| | 13 | -1.834 | 1.544 |
| | 14 | 0.199 | 1.060 |
| | 15 | -3.091 | 1.143 |
| | 16 | 0.154 | 1.144 |
| | 17 | 0.013 | 1.204 |
| | 18 | 1.780 | 1.194 |
| | 19 | 0.093 | 1.453 |
| | 20 | -1.147 | 1.779 |
| | 21 | 1.433 | 1.252 |

Together with supplied PDB files, the contributions for displaced water molecules can be determined.

**Table S13.** Results from the hydration site analysis using WATsite for the MR.

| Site | Hydration site | Enthalpy ΔH (kcal/mol) | Entropy -T*ΔS (kcal/mol) |
|---|---|---|---|
| AF-2 | 1 | -1.166 | 1.477 |
| | 2 | -0.375 | 1.303 |
| | 3 | -0.090 | 1.126 |
| | 4 | -2.637 | 1.218 |
| | 5 | 0.793 | 1.575 |
| | 6 | 0.478 | 2.968 |
| | 7 | -0.069 | 0.927 |
| | 8 | -1.421 | 1.326 |
| | 9 | 0.037 | 1.172 |
| | 10 | -1.355 | 1.187 |
| | 11 | -0.162 | 1.219 |
| | 12 | -2.835 | 1.126 |
| | 13 | 1.587 | 1.051 |
| | 14 | -0.757 | 1.146 |
| | 15 | -0.114 | 1.189 |
| | 16 | -1.896 | 3.226 |
| | 17 | -0.150 | 1.166 |
| | 18 | -0.687 | 1.048 |
| | 19 | 2.746 | 2.030 |
| | 20 | 3.404 | 1.203 |
| | 21 | 3.343 | 1.942 |
| | 22 | 0.373 | 2.113 |
| | 23 | -3.081 | 1.464 |
| | 24 | 0.787 | 2.502 |
| | 25 | 0.249 | 1.435 |
| | 26 | 0.233 | 1.540 |
| BF-3 | 1 | 0.423 | 1.414 |
| | 2 | -0.074 | 1.423 |
| | 3 | -0.038 | 1.282 |
| | 4 | -2.404 | 2.225 |
| | 5 | 0.107 | 1.129 |
| | 6 | 2.132 | 1.807 |
| | 7 | 0.590 | 1.446 |
| | 8 | -1.245 | 1.665 |
| | 9 | -0.117 | 1.253 |
| | 10 | -0.234 | 1.883 |
| | 11 | -1.503 | 2.347 |
| | 12 | -1.689 | 2.307 |
| | 13 | -2.423 | 1.259 |
| | 14 | -2.835 | 1.377 |
| | 15 | -2.114 | 2.422 |
| | 16 | 0.308 | 0.999 |
| | 17 | -2.694 | 1.385 |
| | 18 | -0.889 | 1.221 |
| | 19 | -1.028 | 0.926 |
| | 20 | -0.138 | 1.740 |
| | 21 | 0.422 | 1.058 |
| | 22 | 2.315 | 1.752 |
| | 23 | -2.266 | 1.838 |
| | 24 | -1.022 | 1.392 |
| | 25 | 1.550 | 1.128 |
| | 26 | 0.220 | 1.879 |
| | 27 | -1.076 | 1.350 |

Together with supplied PDB files, the contributions for displaced water molecules can be determined.

**Table S14.** Results from the hydration site analysis using WATsite for the PR.

| Site | Hydration site | Enthalpy ΔH (kcal/mol) | Entropy -T*ΔS (kcal/mol) |
|---|---|---|---|
| AF-2 | 1 | 1.899 | 1.136 |
| | 2 | 1.525 | 1.982 |
| | 3 | 0.082 | 1.417 |
| | 4 | 0.493 | 1.025 |
| | 5 | -0.078 | 1.647 |
| | 6 | -0.241 | 1.120 |
| | 7 | -0.589 | 1.269 |
| | 8 | 2.706 | 1.177 |
| | 9 | -0.851 | 0.998 |
| | 10 | 0.256 | 2.410 |
| | 11 | 2.686 | 1.259 |
| | 12 | -0.800 | 1.389 |
| | 13 | -0.218 | 1.239 |
| | 14 | 0.039 | 1.163 |
| | 15 | 1.101 | 1.005 |
| | 16 | 1.029 | 1.212 |
| | 17 | -0.487 | 1.047 |
| | 18 | 1.156 | 2.287 |
| | 19 | 3.025 | 1.309 |
| | 20 | 2.006 | 1.195 |
| | 21 | 0.183 | 0.881 |
| | 22 | 5.526 | 1.842 |
| | 23 | 0.572 | 1.643 |
| | 24 | 0.346 | 1.279 |
| | 25 | 0.490 | 1.375 |
| | 26 | -0.080 | 1.364 |
| | 27 | -0.750 | 1.391 |
| | 28 | 0.912 | 2.620 |
| BF-3 | 1 | -1.176 | 2.282 |
| | 2 | -0.630 | 1.493 |
| | 3 | -0.173 | 1.252 |
| | 4 | -2.577 | 1.573 |
| | 5 | -2.831 | 1.361 |
| | 6 | -2.604 | 1.564 |
| | 7 | -1.280 | 1.581 |
| | 8 | -1.544 | 2.422 |
| | 9 | -0.169 | 1.246 |
| | 10 | -1.239 | 1.657 |
| | 11 | -2.005 | 2.672 |
| | 12 | -0.481 | 1.416 |
| | 13 | 2.363 | 1.439 |
| | 14 | -1.456 | 1.780 |
| | 15 | -2.933 | 4.050 |
| | 16 | -1.956 | 1.513 |
| | 17 | 0.748 | 0.992 |
| | 18 | 0.497 | 0.954 |
| | 19 | -0.062 | 1.049 |
| | 20 | -1.115 | 1.695 |
| | 21 | 0.474 | 1.569 |
| | 22 | -3.270 | 1.340 |
| | 23 | 0.711 | 1.106 |
| | 24 | 0.355 | 1.318 |
| | 25 | 0.800 | 1.119 |
| | 26 | -0.977 | 1.029 |
| | 27 | -0.462 | 1.466 |
| | 28 | -0.014 | 1.321 |
| | 29 | 0.298 | 1.286 |
| | 30 | -2.060 | 2.165 |
| | 31 | -0.179 | 3.041 |

Together with supplied PDB files, the contributions for displaced water molecules can be determined.

**Table S15.** Results from the hydration site analysis using WATsite for the TRα.

| Site | Hydration site | Enthalpy ΔH (kcal/mol) | Entropy -T*ΔS (kcal/mol) |
|---|---|---|---|
| AF-2 | 1 | -2.281 | 1.745 |
| | 2 | -0.881 | 1.467 |
| | 3 | -0.209 | 1.044 |
| | 4 | 0.073 | 1.066 |
| | 5 | 1.593 | 1.456 |
| | 6 | -0.263 | 0.945 |
| | 7 | -0.385 | 1.312 |
| | 8 | -1.648 | 2.518 |
| | 9 | 1.283 | 2.482 |
| | 10 | -1.949 | 1.531 |
| | 11 | 1.170 | 1.084 |
| | 12 | 0.612 | 2.079 |
| | 13 | 0.045 | 1.495 |
| | 14 | -0.874 | 0.987 |
| | 15 | 0.317 | 1.213 |
| | 16 | 1.138 | 1.210 |
| | 17 | -3.192 | 1.621 |
| | 18 | 1.022 | 1.079 |
| | 19 | -1.673 | 2.313 |
| | 20 | -2.714 | 1.572 |
| | 21 | -2.047 | 1.568 |
| | 22 | 2.491 | 1.467 |
| | 23 | -0.582 | 1.076 |
| | 24 | -0.509 | 1.492 |
| | 25 | -0.282 | 1.453 |
| | 26 | -0.482 | 1.439 |
| BF-3 | 1 | -1.910 | 1.147 |
| | 2 | 0.699 | 0.996 |
| | 3 | -0.006 | 1.014 |
| | 4 | 0.149 | 2.436 |
| | 5 | -1.087 | 0.928 |
| | 6 | -0.719 | 1.004 |
| | 7 | -2.322 | 2.107 |
| | 8 | -0.054 | 1.250 |
| | 9 | -2.651 | 1.857 |
| | 10 | -0.151 | 0.993 |
| | 11 | 0.695 | 0.940 |
| | 12 | 0.144 | 4.222 |
| | 13 | 1.439 | 2.201 |
| | 14 | -1.717 | 1.053 |
| | 15 | 0.631 | 1.180 |
| | 16 | -0.594 | 1.340 |
| | 17 | -0.126 | 1.164 |
| | 18 | 0.259 | 1.302 |
| | 19 | -4.333 | 2.419 |
| | 20 | -3.912 | 4.797 |
| | 21 | -1.692 | 1.279 |
| | 22 | -1.958 | 1.322 |
| | 23 | 5.827 | 3.775 |
| | 24 | 0.815 | 1.770 |
| | 25 | -1.911 | 2.939 |
| | 26 | 1.430 | 4.353 |
| | 27 | 0.016 | 1.486 |
| | 28 | 3.330 | 3.112 |

Together with supplied PDB files, the contributions for displaced water molecules can be determined.

**Table S16.** Results from the hydration site analysis using WATsite for the TRβ.

| Site | Hydration site | Enthalpy ΔH (kcal/mol) | Entropy -T*ΔS (kcal/mol) |
|---|---|---|---|
| AF-2 | 1 | -0.950 | 2.188 |
| | 2 | 2.440 | 2.059 |
| | 3 | 0.776 | 0.772 |
| | 4 | 1.657 | 1.084 |
| | 5 | -0.851 | 1.706 |
| | 6 | 0.651 | 1.147 |
| | 7 | 1.646 | 1.030 |
| | 8 | 2.202 | 1.809 |
| | 9 | 4.439 | 2.164 |
| | 10 | -0.630 | 1.677 |
| | 11 | 0.124 | 1.098 |
| | 12 | 2.192 | 1.177 |
| | 13 | 0.712 | 1.333 |
| | 14 | -0.165 | 1.103 |
| | 15 | 0.053 | 1.359 |
| | 16 | 0.271 | 1.174 |
| | 17 | -0.313 | 1.656 |
| | 18 | -2.557 | 1.708 |
| | 19 | -0.735 | 2.331 |
| | 20 | -2.922 | 1.945 |
| BF-3 | 1 | -0.489 | 1.175 |
| | 2 | 2.328 | 2.076 |
| | 3 | -0.399 | 1.179 |
| | 4 | 2.350 | 1.311 |
| | 5 | 0.439 | 1.970 |
| | 6 | -1.945 | 1.732 |
| | 7 | -0.701 | 1.558 |
| | 8 | -1.152 | 1.157 |
| | 9 | -3.593 | 2.143 |
| | 10 | -0.903 | 2.736 |
| | 11 | -0.823 | 1.223 |
| | 12 | -6.124 | 3.778 |
| | 13 | -0.618 | 1.306 |
| | 14 | -2.101 | 1.378 |
| | 15 | 1.404 | 2.224 |
| | 16 | -1.042 | 2.569 |
| | 17 | -0.930 | 1.257 |
| | 18 | 0.597 | 1.198 |
| | 19 | 0.178 | 1.290 |
| | 20 | 5.749 | 4.000 |
| | 21 | -1.485 | 1.554 |
| | 22 | -4.054 | 2.392 |
| | 23 | 0.961 | 0.967 |
| | 24 | 0.264 | 1.209 |
| | 25 | -2.831 | 1.930 |
| | 26 | 0.177 | 1.378 |
| | 27 | -0.084 | 1.265 |
| | 28 | 2.278 | 3.272 |
| | 29 | -0.208 | 1.240 |
| | 30 | 0.152 | 1.578 |
| | 31 | -0.369 | 1.134 |
| | 32 | -0.261 | 2.330 |
| | 33 | -1.878 | 4.147 |
| | 34 | 0.328 | 1.493 |
| | 35 | 2.981 | 1.828 |
| | 36 | -0.110 | 1.351 |
| | 37 | -0.100 | 1.447 |

Together with supplied PDB files, the contributions for displaced water molecules can be determined.

## Molecular Docking

**Figure S11.** Poses obtained from redocking known crystallographic ligands: Glide SP for the AF-2 site

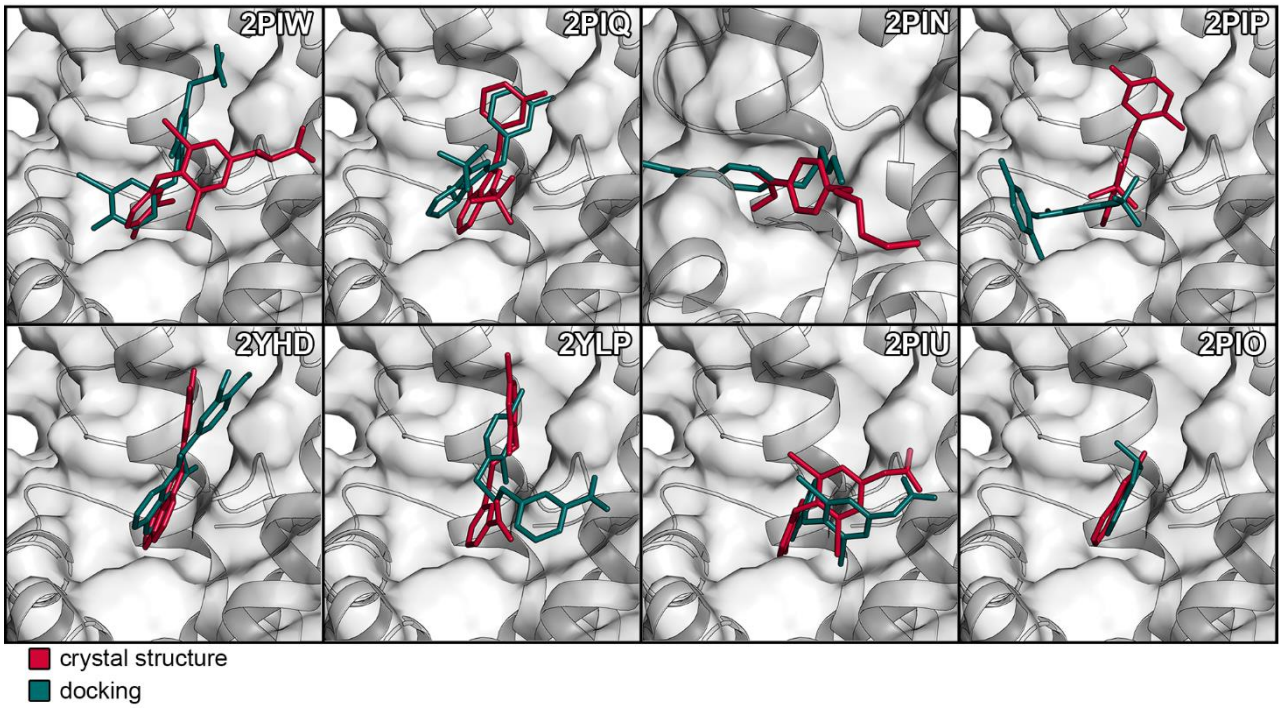



**Figure S12.** Poses obtained from redocking known crystallographic ligands: Glide SP for the BF-3 site.

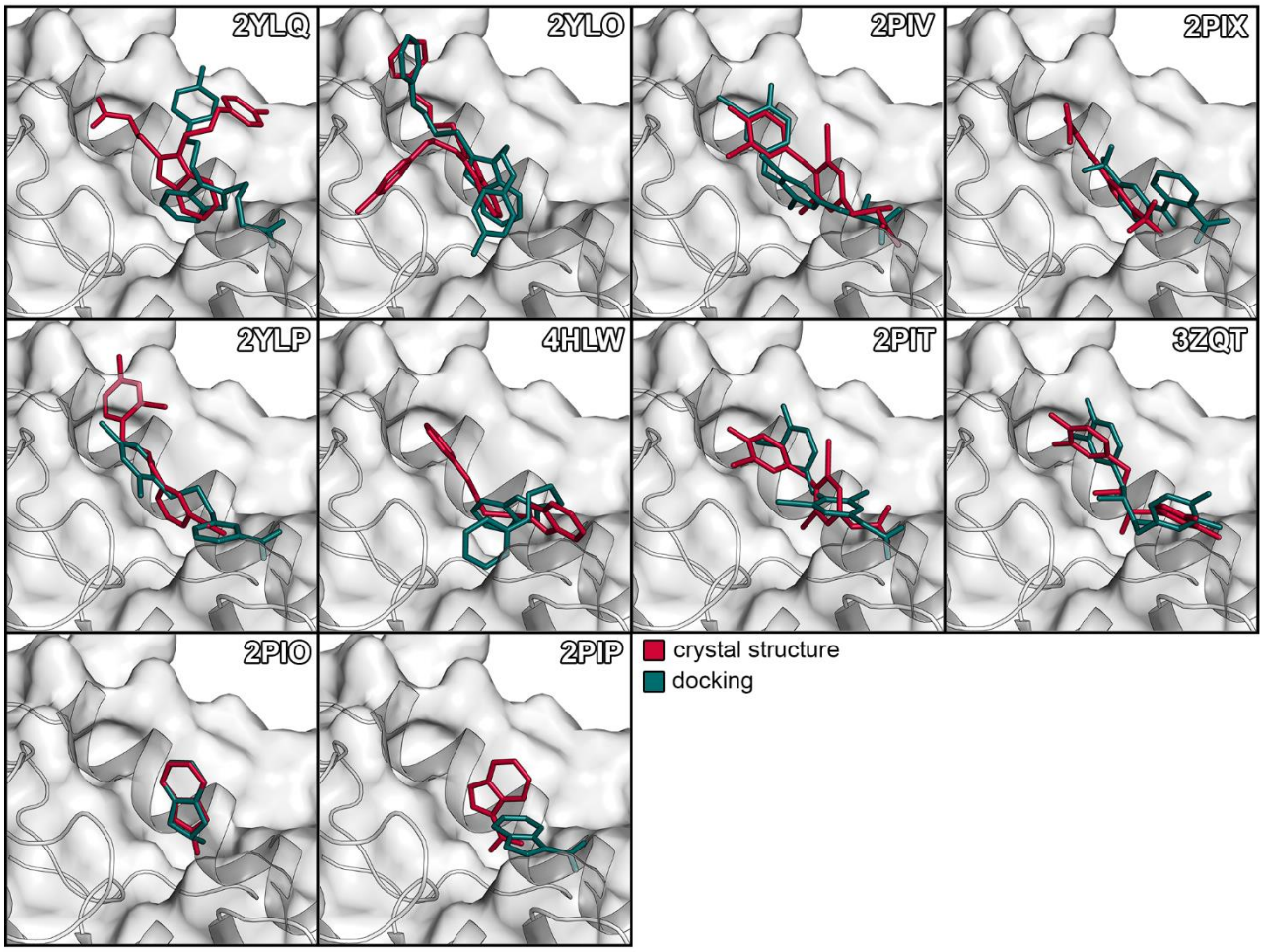


**Figure S13.** Poses obtained from redocking known crystallographic ligands: Glide XP for the AF-2 site.

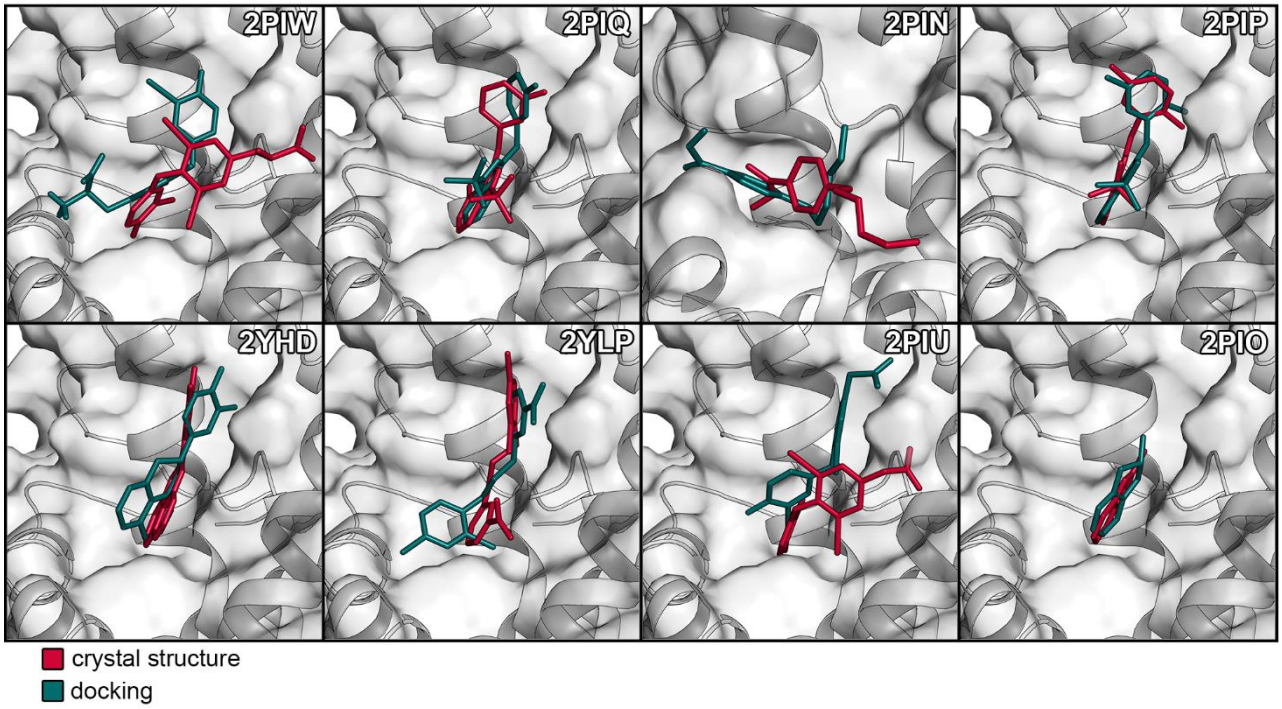



**Figure S14.** Poses obtained from redocking known crystallographic ligands: Glide XP for the AF-2 site.

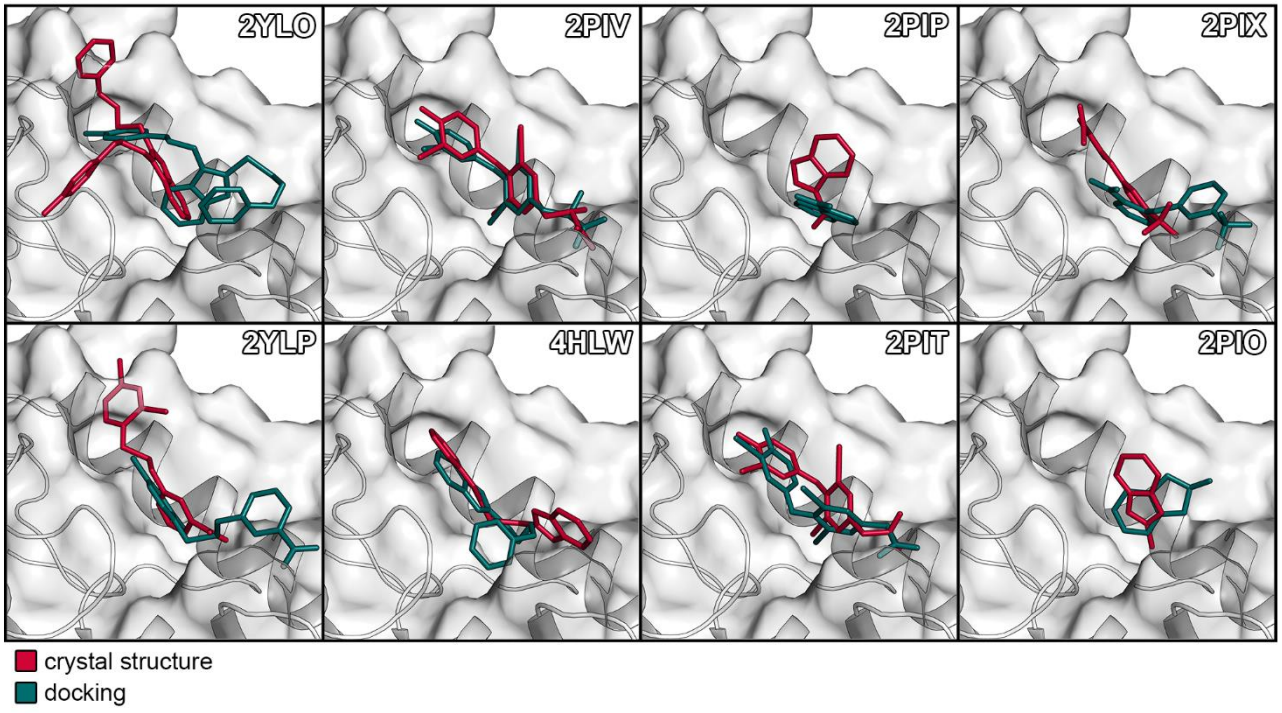
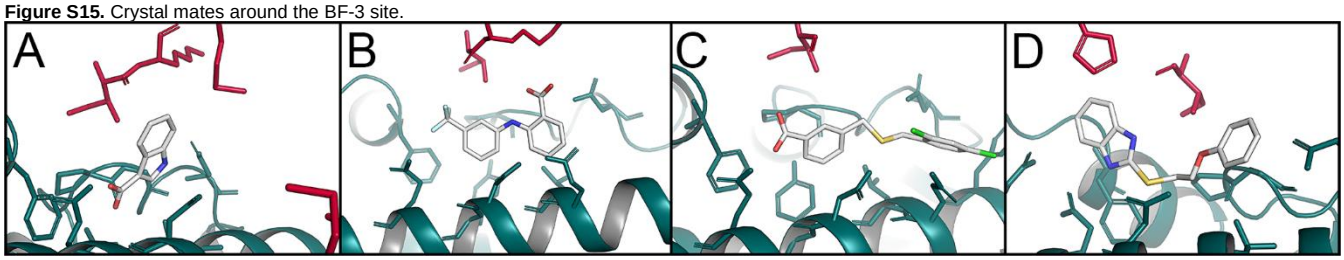


**Table S17.** RMSD obtained from redocking known crystallographic ligands.

| PDB ID | Site | RMSD SP[a] (Å) | RMSD XP[b] (Å) |
|---|---|---|---|
| 2PIQ | AF-2 | 2.11 | 1.19 |
| 2YHD | AF-2 | 1.47 | 1.96 |
| 2PIW | AF-2 | 4.90 | 7.92 |
| 2PIP | AF-2 | 7.10 | 0.84 |
| 2YLP | AF-2 | 4.67 | 7.24 |
| 2PIU | AF-2 | 2.24 | 4.28 |
| 2PIO | AF-2 | 1.67 | 0.92 |
| 2YLQ | BF-3 | 6.76 | n/a[c] |
| 2PIX | BF-3 | 7.46 | 5.06 |
| 2YLP | BF-3 | 5.22 | 7.10 |
| 2PIP | BF-3 | 5.15 | 4.75 |
| 4HLW | BF-3 | 4.78 | 7.00 |
| 2PIO | BF-3 | 1.25 | 3.56 |
| 2PIV | BF-3 | 2.11 | 1.07 |
| 2YLO | BF-3 | 3.83 | 8.22 |
| 2PIT | BF-3 | 2.11 | 1.90 |
| 3ZQT | BF-3 | 1.76 | n/a[c] |
| 2PIN | AF-2 | 4.83 | 4.91 |

[a]Results obtained using SP docking protocol.
[b]Results obtained using XP docking protocol.
[c]No pose was obtained by the applied protocol and specifications.

**Figure S15.** Crystal mates around the BF-3 site.




Crystal mates in the 4 A radius of cocrystallized ligands at the BF-3. Nearby mates were colored red.

**Table S18**. Results from docking the DUD-E dataset against known actives.

| | AR AF-2 | AR BF-3 | ERα AF-2 | ERβ AF-2 | TRα AF-2 | TRβ AF-2 | GR AF-2 |
|---|---|---|---|---|---|---|---|
| Actives | 44 | 87 | 65 | 3 | 28 | 99 | 8 |
| Decoys | 2650 | 4350 | 4957 | 200 | 1450 | 5350 | 450 |
| ROC AUC | 0.75 | 0.76 | 0.71 | 0.85 | 0.45 | 0.55 | 0.87 |

**Figure S16.** Score distributions for the ERα.

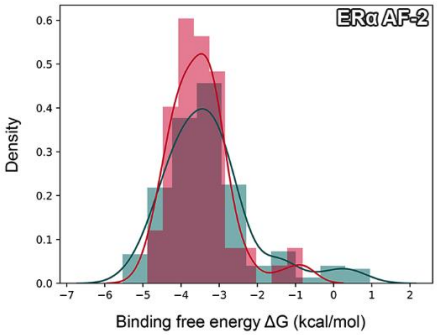



**Figure S17.** Score distributions determined by the Glide XP docking protocol.

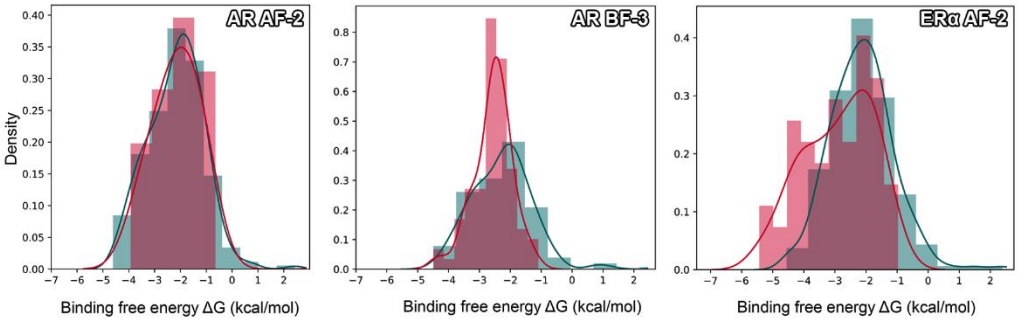
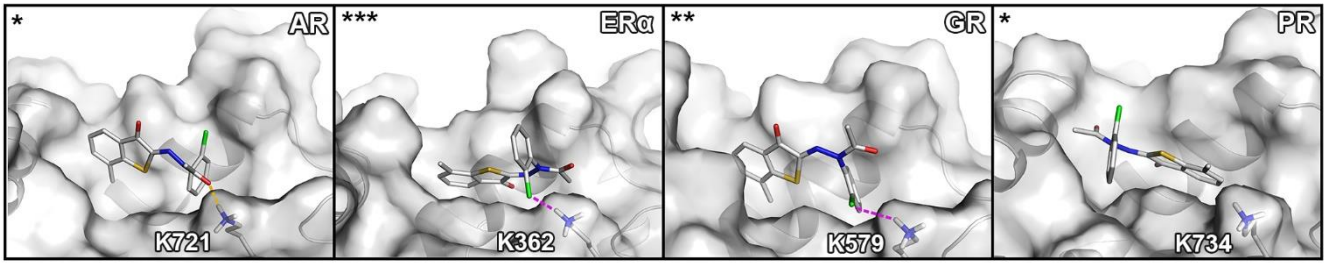



**Figure S18.** VPC16606 in docked to various NRs.

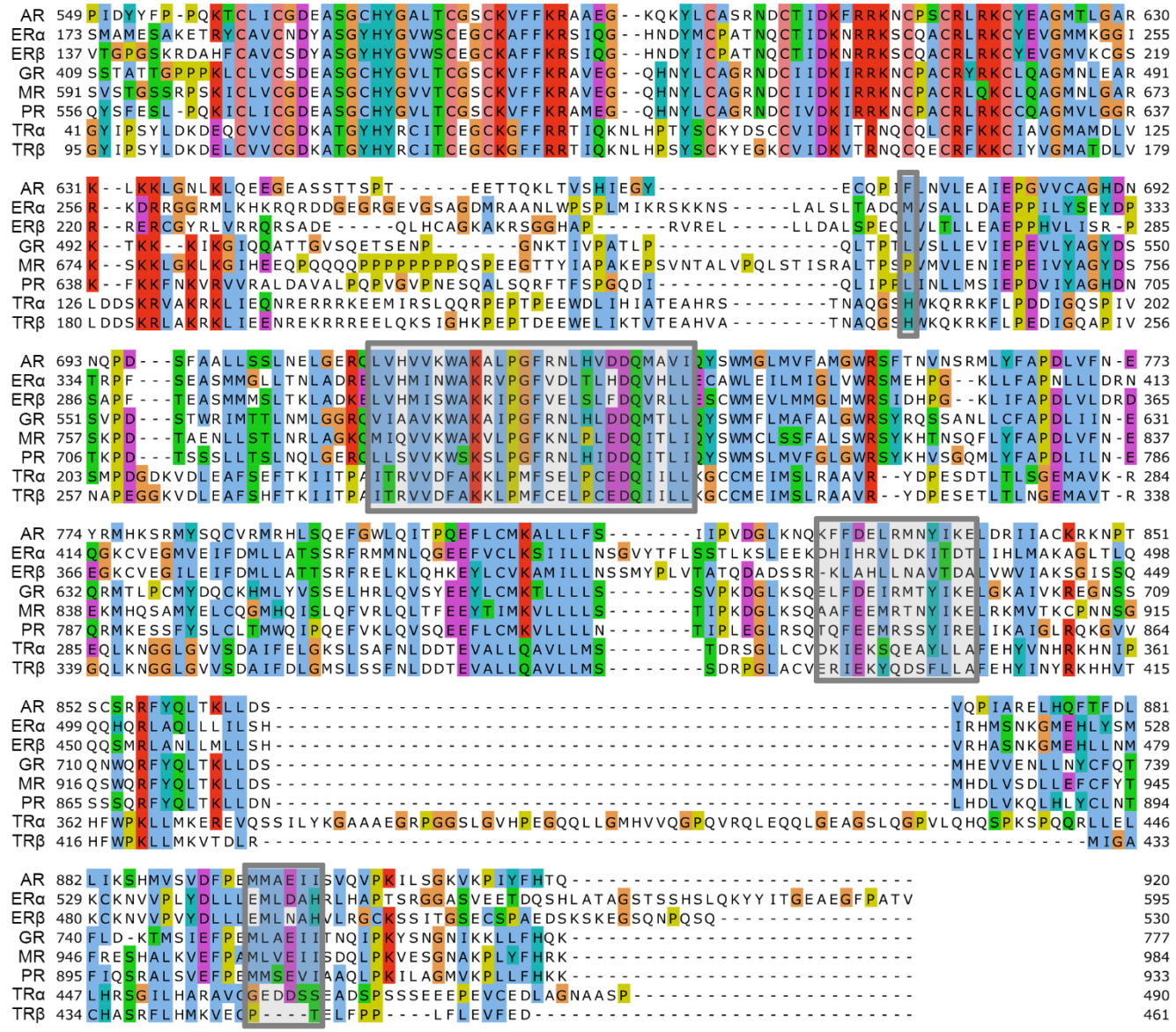



The ERα AF-2 inhibitor VPC166606 was docked into various nuclear receptors. The inhibitory activity measured for each receptor is indicated at the top left by asterisks.

# Supporting Materials and Methods

## Sequence Alignment and Analysis

**Figure S19.** Sequence alignment of all NRs assessed in this study.




Sequence alignment of the NRs considered in this study. Residues of the allosteric sites were indicated with gray boxes.

**Table S19.** Amino acid groups for sequence analysis.

| Group | Amino acids |
|---|---|
| 1 | A, I, L, M, F, W, V, C |
| 2 | N, Q, S, T |
| 3 | E, D |
| 4 | K, R |
| 5 | H, Y |
| 6 | P |
| 7 | G |

The amino acids groups used to determine the degree of conservation according to the ClustalW scheme are shown. The residues are given in single-letter code.

## Ligand Preparation

**Table S20.** Structures prepared for molecular docking.

| # | SMILES code[a] | Site | Reference[b] |
|---|---|---|---|
| 1 | [O-]C(=O)c1cc(ccc1)CSCc2c(Cl)cc(Cl)cc2 | AR AF-2 | [1] |
| 2 | CCOc1c(O)ccc(c1)C(Nc2ccc3)Nc4cccc3c24 | AR AF-2 | [2] |
| 3 | c12c3cccc1NC(Nc2ccc3)c4ccc(O)cc4 | AR AF-2 | [2] |
| 4 | COc1c(O)ccc(c1)C(Nc2ccc3)Nc4cccc3c24 | AR AF-2 | [2] |
| 5 | COc1c(O)cc(cc1)C(Nc2ccc3)Nc4cccc3c24 | AR AF-2 | [2] |
| 6 | c12c3cccc1NC(Nc2ccc3)c(c4)ccc(O)c4O | AR AF-2 | [2] |
| 7 | [O-]C(=O)c1c(O)cc(cc1)N\N=C\2C(=O)N(N=C2C)c3ccccc3 | AR AF-2 | [2] |
| 8 | Cc(c1)[nH]c(c12)cccc2 | AR AF-2 | [3] |
| 9 | Nc1ncnc(c12)n(C(C)(C)C)nc2Cc3c(C)ccc(C)c3 | AR AF-2 | [3] |
| 10 | c1cccc(c1C([O-])=O)Nc(c(Cl)c2C)c(Cl)cc2 | AR AF-2 | [3] |
| 11 | Nc1ncnc(c12)n(C(C)(C)C)nc2Cc3cc(O)ccc3 | AR AF-2 | [3] |
| 12 | [O-]C(=O)[C@@H]([NH3+])Cc(cc1I)cc(I)c1Oc(cc2)cc(I)c2O | AR AF-2 | [3] |
| 13 | c1cccc(c1C([O-])=O)Nc(c2C)cccc2Cl | AR AF-2 | [3] |
| 14 | [O-]C(=O)Cc(cc1I)cc(I)c1Oc(cc2)cc(I)c2O | AR AF-2 | [3] |
| 15 | c1ccccc1CNc(n2)nc(NCC(C)C)cc2CCc3ccccc3 | AR AF-2 | [5] |
| 16 | CC(C)CCc1cc(NCC(C)C)nc(n1)NCC(C)C | AR AF-2 | [5] |
| 17 | CC(C)CNC(=N1)NC(CCC(C)C)C=C1NCc2ccccc2 | AR AF-2 | [5] |
| 18 | c1ccccc1CCC(NC(=N2)NCC(C)C)C=C2NCc3ccccc3 | AR AF-2 | [5] |
| 19 | CC(C)CNc(n1)nc(NCC(C)C)cc1CCc2cccc(c23)cccc3 | AR AF-2 | [5] |
| 20 | c1ccccc1CCc2cc(NCC(C)C)nc(n2)NCc3cccc(c34)cccc4 | AR AF-2 | [5] |
| 21 | c1ccccc1CNC2=CC(NC(=N2)NCC(C)C)CCc3cccc(c34)cccc4 | AR AF-2 | [5] |
| 22 | c1ccccc1CNc(n2)nc(NCC(C)C)cc2CCc3cccc(c34)cccc4 | AR AF-2 | [5] |
| 23 | c1cccc(c12)cccc2CNc(n3)nc(NCC(C)C)cc3CCc4cccc(c45)cccc5 | AR AF-2 | [5] |
| 24 | c1cccc(c12)cccc2CNC(=N3)NC(CCC(C)C)C=C3NCc4cccc(c45)cccc5 | AR AF-2 | [5] |
| 25 | c1ccccc1CNc2cc(NCc3ccccc3)nc(n2)NCc4ccccc4 | AR AF-2 | [5] |
| 26 | c1cccc(c12)cccc2CCC(C=C3NCc4ccccc4)NC(=N3)NCc5ccccc5 | AR AF-2 | [5] |
| 27 | c1cccc(c12)cccc2CCC(NC(=N3)NCc4ccccc4)C=C3NCc5cccc(c56)cccc6 | AR AF-2 | [5] |
| 28 | c1cccc(c12)cc(O)c(c2)C(=O)N\N=C\c(c3)c(O)cc(c34)cccc4 | AR AF-2 | [4] |
| 29 | c1cccc(c12)cc(O)c(c2)C(=O)N\N=C\c3c(O)ccc(Br)c3 | AR AF-2 | [4] |
| 30 | COc(c1)c(O)c(OC)cc1/C=N/NC(=O)c(c2)oc(c23)ccc4c3cccc4 | AR AF-2 | [4] |
| 31 | c1cccc2c1ccc(c23)oc(c3)C(=O)N\N=C\c4ccc(cc4)OCCC | AR AF-2 | [4] |
| 32 | c1ccccc1CCC(=O)C2=C([O-])C(=O)N(Cc3ccccc3)[C@@H]2c4cc(F)ccc4 | AR AF-2 | [9] |
| 33 | c1ccccc1CCC(=O)C2=C([O-])C(=O)N(Cc3ccccc3)[C@H]2c4cc(F)ccc4 | AR AF-2 | [9] |
| 34 | c1cccc(c12)cc([O-])c(c2)C(=O)N\N=C\c3ccccc3 | AR AF-2 | [10] |
| 35 | c1cccc(c12)cc([O-])c(c2)C(=O)N\N=C\c3c(O)ccc(c3)O | AR AF-2 | [10] |
| 36 | c1cccc(c12)cc([O-])c(c2)C(=O)N\N=C\c3c(O)ccc(c3)OC | AR AF-2 | [10] |
| 37 | [O-]C(=O)c1cc(c(O)cc1)/C=N/NC(=O)c(c2)c([O-])cc(c23)cccc3 | AR AF-2 | [10] |
| 38 | c1cccc(c12)cc([O-])c(c2)C(=O)N\N=C\c(c([O-])cc3)cc3C(=O)OC | AR AF-2 | [10] |
| 39 | c1cccc(c12)cc([O-])c(c2)C(=O)N\N=C\c3c([O-])ccc(c3)[N+]([O-])=O | AR AF-2 | [10] |
| 40 | c1cccc(c12)cc([O-])c(c2)C(=O)N\N=C\c3c(O)c(C)ccc3 | AR AF-2 | [10] |
| 41 | c1cccc(c12)cc([O-])c(c2)C(=O)N\N=C\c3c(O)c(OC)ccc3 | AR AF-2 | [10] |
| 42 | CC(C)(C)OC(=O)NCC(=O)Nc(cc1)c(OCc2ccccc2)cc1C(=O)Nc(cc3)c(cc3C(=O)OCC=C)OCc4ccccc4 | AR AF-2 | [31] |
| 43 | CC(C)COc(c([N+]([O-])=O)cc1)cc1C(=O)Nc(cc2)c(OCC(C)C)cc2C(=O)OC | AR AF-2 | [31] |
| 44 | CC(=O)c1cc(ccc1)S(=O)(=O)Nc(ccc2)cc2-c3cc[nH]n3 | AR AF-2 | [32] |
| 45 | [O-]C(=O)c1cc(ccc1)CSCc2c(Cl)cc(Cl)cc2 | AR BF-3 | [6] |
| 46 | [O-]C(=O)c1cc(ccc1)CSc2c(Cl)cc(Cl)cc2 | AR BF-3 | [6] |
| 47 | [O-]C(=O)CCSc(n1)n(c(c12)cccc2)CCOc(cc3)ccc3C | AR BF-3 | [6] |
| 48 | Cc1ccc(cc1)OCCn(c(c23)cccc2)c(n3)SCCOc4ccccc4 | AR BF-3 | [6] |

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| 49 | c1cc(O)c(O)cc1C[C@H](C)[C@@H](C)Cc2cc(O)c(O)cc2 | AR BF-3 | [6] |
| 50 | CC(=O)c(cc1)cc2c1N[C@@H]([C@@H]([C@@H]23)CC=C3)c(cc4)ccc4C(=O)OC | AR BF-3 | [6] |
| 51 | CCOC(=O)c(cc1)cc2c1N[C@@H]([C@H]([C@@H]23)CC=C3)c4ccccc4 | AR BF-3 | [6] |
| 52 | CN(C)S(=O)(=O)c(cc1)cc2c1N[C@@H]([C@H]([C@H]23)CC=C3)c4ccc(Br)cc4 | AR BF-3 | [6] |
| 53 | c1cc(O)c(O)cc1C(=O)CSc([nH]c2=O)nc(c23)cccc3 | AR BF-3 | [6] |
| 54 | [O-]C(=O)/C=C/c1c(C)n(c(C)c1)-c(c2)ccc(c23)OCO3 | AR BF-3 | [6] |
| 55 | CC(C)OC(=O)Cn(c(c12)cccc1)c(n2)SCCOc(cc3C)ccc3 | AR BF-3 | [11] |
| 56 | c1cccc(c12)n(CCOC)c(n2)SCCOc(cc3C)ccc3 | AR BF-3 | [11] |
| 57 | CC(C)OC(=O)Cn(c(c12)cccc1)c(n2)SCCOc(cc3)ccc3C | AR BF-3 | [11] |
| 58 | CCOC(=O)Cn(c(c12)cccc1)c(n2)SCCOc(c3C)cccc3 | AR BF-3 | [11] |
| 59 | Cc1ccc(cc1)OCCn(c(c23)cccc2)c(n3)SCCOc(cc4)ccc4CC | AR BF-3 | [11] |
| 60 | c1cccc(c12)n(CCOC)c(n2)SCCOc(cc3)ccc3C | AR BF-3 | [11] |
| 61 | CC(C)OC(=O)Cn(c(c12)cccc1)c(n2)SCCOc(c3)ccc(C)c3C | AR BF-3 | [11] |
| 62 | c1cccc(c12)n(CC(=O)OC)c(n2)SCCOc(cc3C)ccc3 | AR BF-3 | [11] |
| 63 | Cc1ccc(cc1)OCCSc(n2)n(CC)c(c23)cccc3 | AR BF-3 | [11] |
| 64 | CCOC(=O)Cn(c(c12)cccc1)c(n2)SCCOc(c3)ccc(C)c3C | AR BF-3 | [11] |
| 65 | Cc1ccc(cc1)OCCSc(n2)n(C)c(c23)cccc3 | AR BF-3 | [11] |
| 66 | CCOC(=O)Cn(c(c12)cccc1)c(n2)SCCOc(cc3)ccc3CC | AR BF-3 | [11] |
| 67 | c1cccc(c12)n(CC([O-])=O)c(n2)SCCOc(cc3C)ccc3 | AR BF-3 | [11] |
| 68 | c1ccccc1OCCSc(n2)[nH]c(c23)cccc3 | AR BF-3 | [11] |
| 69 | c1ccccc1OCCSc(n2)n(CC)c(c23)cccc3 | AR BF-3 | [11] |
| 70 | c1ccccc1CCCSc(n2)[nH]c(c23)cccc3 | AR BF-3 | [11] |
| 71 | c1ccccc1CCSc(n2)[nH]c(c23)cccc3 | AR BF-3 | [11] |
| 72 | c1cccc(c1C)OCCSc(n2)[nH]c(c23)cccc3 | AR BF-3 | [11] |
| 73 | Cc1cc(ccc1)OCCSc(n2)[nH]c(c23)cccc3 | AR BF-3 | [11] |
| 74 | Cc1ccc(cc1)OCCSc(n2)[nH]c(c23)cccc3 | AR BF-3 | [11] |
| 75 | c1ccc(C)c(c1C)OCCSc(n2)[nH]c(c23)cccc3 | AR BF-3 | [11] |
| 76 | c1ccc(Cl)cc1OCCSc(n2)[nH]c(c23)cccc3 | AR BF-3 | [11] |
| 77 | c1cc(Cl)ccc1OCCSc(n2)[nH]c(c23)cccc3 | AR BF-3 | [11] |
| 78 | c1cc(S(=O)(=O)N)ccc1OCCSc(n2)[nH]c(c23)cccc3 | AR BF-3 | [11] |
| 79 | c1ccccc1OCCSc(c2)[nH]c(c23)cccc3 | AR BF-3 | [11] |
| 80 | c1ccccc1OCCSc(c2)[nH]c(c23)c(S(=O)(=O)N)ccc3 | AR BF-3 | [11] |
| 81 | c1ccccc1\C=C\c2c[nH]c(c23)cccc3 | AR BF-3 | [12] |
| 82 | c1cccc(c1C(F)(F)F)\N=C\c2c[nH]c(c23)cccc3 | AR BF-3 | [12] |
| 83 | c1cc(Cl)cc(Cl)c1\N=C\c2c[nH]c(c23)cccc3 | AR BF-3 | [12] |
| 84 | Cc1cc(ccc1)\N=C\c2c[nH]c(c23)cccc3 | AR BF-3 | [12] |
| 85 | c1ccc(OC)cc1\N=C\c2c[nH]c(c23)cccc3 | AR BF-3 | [12] |
| 86 | c1cccc(c12)[nH]cc2/C=N/c3cccc(C)c3C | AR BF-3 | [12] |
| 87 | Clc1cccc(Cl)c1\N=C\c2c[nH]c(c23)cccc3 | AR BF-3 | [12] |
| 88 | c1cccc(OC)c1\N=C\c2c[nH]c(c23)cccc3 | AR BF-3 | [12] |
| 89 | Clc1cccc(c1Cl)\N=C\c2c[nH]c(c23)cccc3 | AR BF-3 | [12] |
| 90 | Brc1cccc(c1Br)\N=C\c2c[nH]c(c23)cccc3 | AR BF-3 | [12] |
| 91 | c1cccc(c1C(F)(F)F)\N=N\c2c[nH]c(c23)cccc3 | AR BF-3 | [12] |
| 92 | c1cccc(c12)[nH]cc2/N=N/c3ccccc3 | AR BF-3 | [12] |
| 93 | c1cccc(c12)[nH]cc2/N=N/c3c(Cl)cccc3 | AR BF-3 | [12] |
| 94 | Cc1c(C)cccc1\N=N\c2c[nH]c(c23)cccc3 | AR BF-3 | [12] |
| 95 | c1cccc(c12)[nH]cc2/N=N/c3cc(Cl)ccc3 | AR BF-3 | [12] |
| 96 | Cc1cc(ccc1)\N=N\c2c[nH]c(c23)cccc3 | AR BF-3 | [12] |
| 97 | c1cccc(c12)[nH]cc2/N=N/c(cccc3)c3-c4ccccc4 | AR BF-3 | [12] |
| 98 | c1cccc(c12)[nH]cc2-c(c3)[nH]c(c34)cccc4 | AR BF-3 | [12] |
| 99 | c1cccc(c12)n(C)c(c2)-c3cn(C)c(c34)cccc4 | AR BF-3 | [12] |

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| 100 | c1cccc(c12)[nH]cc2C([C@@H]3N=O)=Nc(c34)cccc4 | AR BF-3 | [12] |
| 101 | c1cccc(c12)[nH]cc2-c(n3)[nH]c(c34)cccc4 | AR BF-3 | [12] |
| 102 | c1cccc(c12)[nH]cc2C(C3)Cc(c34)cccc4 | AR BF-3 | [12] |
| 103 | c1cccc(c12)C[C@H]([C@@H]2C)c3c[nH]c(c34)cccc4 | AR BF-3 | [12] |
| 104 | o1c(Br)ccc1CN(C)C(=O)c(c2)[nH]c(c23)cc(F)cc3 | AR BF-3 | [7] |
| 105 | c1c(F)ccc(c12)[nH]c(c2)C(=O)N(C)Cc3ccc(o3)C | AR BF-3 | [7] |
| 106 | c1ccccc1CN(CCC#N)C(=O)c(c2)[nH]c(c23)cccc3 | AR BF-3 | [7] |
| 107 | o1cccc1CN(CCOC)C(=O)c(c2)[nH]c(c23)ccc(F)c3 | AR BF-3 | [7] |
| 108 | o1cccc1CN(C(C)C)C(=O)c(c2)[nH]c(c23)ccc(C(F)(F)F)c3 | AR BF-3 | [7] |
| 109 | o1cccc1CN(Cc2ccco2)C(=O)c(c3)[nH]c(c34)cc(F)cc4 | AR BF-3 | [7] |
| 110 | s1c(Br)ccc1CN(C)C(=O)c(c2)[nH]c(c23)cc(F)cc3 | AR BF-3 | [7] |
| 111 | s1cccc1CN(C)C(=O)c(c2)[nH]c(c23)cc(F)cc3 | AR BF-3 | [7] |
| 112 | c1cccc(c12)[nH]c(c2)C(=O)N(C(C)C)Cc3ccc(o3)C | AR BF-3 | [7] |
| 113 | c1cc(C)cc(c12)[nH]c(c2)C(=O)N(C(C)C)Cc3ccc(o3)C | AR BF-3 | [7] |
| 114 | Cc(c1)ccc(c12)[nH]c(c2)C(=O)N(C(C)C)Cc3ccc(o3)C | AR BF-3 | [7] |
| 115 | o1cccc1CN(C(C)C)C(=O)c(c2)[nH]c(c23)ccc(C)c3 | AR BF-3 | [7] |
| 116 | c1c(F)ccc(c12)[nH]c(c2)C(=O)N(C(C)C)Cc3ccc(o3)C | AR BF-3 | [7] |
| 117 | o1cccc1CN(C(C)C)C(=O)c(c2)[nH]c(c23)cc(C)cc3 | AR BF-3 | [7] |
| 118 | c1ccc(F)c(c12)[nH]c(c2)C(=O)N(C(C)C)Cc3ccc(o3)C | AR BF-3 | [7] |
| 119 | c1cc(F)cc(c12)[nH]c(c2)C(=O)N(C(C)C)Cc3ccc(o3)C | AR BF-3 | [7] |
| 120 | o1cccc1CN(C(C)C)C(=O)c(c2)[nH]c(c23)ccc(F)c3 | AR BF-3 | [7] |
| 121 | o1cccc1CN(C(C)C)C(=O)c(c2)[nH]c(c23)cc(F)cc3 | AR BF-3 | [7] |
| 122 | c1ccc(C)c(c12)[nH]cc2-c(cc3)nc(c34)cccc4 | AR BF-3 | [13] |
| 123 | Cc(c1)[nH]c(c12)cccc2 | AR BF-3 | [3] |
| 124 | c1cccc(c1C([O-])=O)Nc(cc2C(F)(F)F)ccc2 | AR BF-3 | [3] |
| 125 | [O-]C(=O)c1c[nH]c(c12)cccc2 | AR BF-3 | [3] |
| 126 | c1cccc(c1C([O-])=O)Nc(c(Cl)c2C)c(Cl)cc2 | AR BF-3 | [3] |
| 127 | [O-]C(=O)[C@@H]([NH3+])Cc(cc1I)cc(I)c1Oc(cc2)cc(I)c2O | AR BF-3 | [3] |
| 128 | c1cccc(c1C([O-])=O)Nc(c2C)cccc2Cl | AR BF-3 | [3] |
| 129 | [O-]C(=O)Cc(cc1I)cc(I)c1Oc(cc2)cc(I)c2O | AR BF-3 | [3] |
| 130 | NC(=O)Cc1cn(CC(C)C)c(c12)ccc(c2)-c3c(OC)cccc3 | AR BF-3 | [34] |
| 131 | s1cccc1C(=O)Nc(n(n2)-c(c3C)cccc3)cc2-c4c(Cl)cccc4 | AR BF-3 | [34] |
| 132 | CC(C)(C)c1cc(ccn1)-c(c2CC(C)C)n(c(=O)c([O-])c2)Cc3ccccc3 | ERα AF-2 | [14] |
| 133 | CC(C)(C)c1cc(ccn1)-c(c2CC(C)C)n(c(=O)c(c2)O)Cc3ccccc3 | ERα AF-2 | [14] |
| 134 | c1cccc(Cl)c1N(C(=O)C)\N=C(\C2=O)Sc(c23)c(C)ccc3 | ERα AF-2 | [33] |
| 135 | C1CCCCC1Cc2c(OCC(=O)OCC)ccc(c2)-c3ccc(cc3)OCC[NH+](C)C | ERα AF-2 | [15] |
| 136 | CC(C)CNc(cc1CC)nc(n1)NCC(C)C | ERα AF-2 | [5] |
| 137 | c1ccccc1CNc(n2)nc(NCC(C)C)cc2CCc3ccccc3 | ERα AF-2 | [5] |
| 138 | CC(C)CCc1cc(NCC(C)C)nc(n1)NCC(C)C | ERα AF-2 | [5] |
| 139 | CC(C)CNC(=N1)NC(CCC(C)C)C=C1NCc2ccccc2 | ERα AF-2 | [5] |
| 140 | c1ccccc1CCC(NC(=N2)NCC(C)C)C=C2NCc3ccccc3 | ERα AF-2 | [5] |
| 141 | CC(C)CNc(n1)nc(NCC(C)C)cc1CCc2cccc(c23)cccc3 | ERα AF-2 | [5] |
| 142 | c1ccccc1CCc2cc(NCC(C)C)nc(n2)NCc3cccc(c34)cccc4 | ERα AF-2 | [5] |
| 143 | c1ccccc1CNC2=CC(NC(=N2)NCC(C)C)CCc3cccc(c34)cccc4 | ERα AF-2 | [5] |
| 144 | COC(=O)C(C(=O)OC)=C[C@](C)([C@@H]12)C[C@H](C=C1)[C@H](C2)C(C)(C)CCNC(=O)CCC(C)C | ERα AF-2 | [30] |
| 145 | COC(=O)C(C(=O)OC)C[C@](C)([C@H]12)C[C@H](CC2)[C@H](C1)C(C)(C)CCNC(=O)CCC(C)C | ERα AF-2 | [30] |
| 146 | COC(=O)[C@@H](C([O-])=O)C[C@](C)([C@H]12)C[C@H](CC2)[C@H](C1)C(C)(C)CCNC(=O)CCC(C)C | ERα AF-2 | [30] |
| 147 | c1ccccc1COC(=O)N[C@H](C(=O)OC)C[C@](C)([C@H]23)C[C@H](CC3)[C@H](C2)C(C)(C)CCNC(=O)CCC(C)C | ERα AF-2 | [30] |
| 148 | COC(=O)[C@@H](N)C[C@](C)([C@H]12)C[C@H](CC2)[C@H](C1)C(C)(C)CCNC(=O)CCC(C)C | ERα AF-2 | [30] |
| 149 | CCCCc1c(CC[NH3+])c(CCCC)c(CC[NH3+])c(CCCC)c1CC[NH3+] | ERα AF-2 | [8] |
| 150 | CCCCCc1c(CC[NH3+])c(CCCCC)c(CC[NH3+])c(c1CC[NH3+])CCCCC | ERα AF-2 | [8] |

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| 151 | CCCCCCc1c(CC[NH3+])c(CCCCCC)c(CC[NH3+])c(c1CC[NH3+])CCCCCC | ERα AF-2 | [8] |
| 152 | CC(C)(C)CCc1c(CC[NH3+])c(CCC(C)(C)C)c(CC[NH3+])c(CCC(C)(C)C)c1CC[NH3+] | ERα AF-2 | [8] |
| 153 | c1ccccc1/C=C/c2cc(NCC(C)C)nc(n2)NCC(C)C | ERα AF-2 | [5] |
| 154 | CC(C)CNc(n1)nc(NCC(C)C)cc1CCc2ccccc2 | ERα AF-2 | [5] |
| 155 | c1ccccc1/C=C/C(NC(=N2)NCC(C)C)C=C2NCc3ccccc3 | ERα AF-2 | [5] |
| 156 | c1ccccc1CNc(n2)nc(NCC(C)C)cc2CCc3ccccc3 | ERα AF-2 | [5] |
| 157 | c1ccccc1CCC(NC(=N2)NCC(C)C)C=C2NCc3ccccc3 | ERα AF-2 | [5] |
| 158 | CCCCc1cc(NCCC)nc(n1)NCCC | ERα AF-2 | [5] |
| 159 | CC(C)CCc1cc(NCC(C)C)nc(n1)NCC(C)C | ERα AF-2 | [5] |
| 160 | c1ccccc1CNC(=N2)NC(CCC(C)C)C=C2NCc3ccccc3 | ERα AF-2 | [5] |
| 161 | CC(C)CNc(n1)nc(NCC(C)C)cc1CCc2cccc(c23)cccc3 | ERα AF-2 | [5] |
| 162 | CC(C)CNc(cc1CC)nc(n1)NCC(C)C | ERα AF-2 | [5] |
| 163 | CC(C)CCc1cc(NCC(C)C)nc(n1)NCc2ccccc2 | ERα AF-2 | [5] |
| 164 | CC(C)CCc1cc(NCC(C)C)nc(n1)NCc2cccc(c23)cccc3 | ERα AF-2 | [5] |
| 165 | CC(C)CNC(=N1)NC(CCC(C)C)C=C1NCc2ccccc2 | ERα AF-2 | [5] |
| 166 | CC(C)CNC(=N1)NC(CCC(C)C)C=C1NCc2cccc(c23)cccc3 | ERα AF-2 | [5] |
| 167 | CC(C)CNc1cc(NCC(C)C)nc(n1)NCC(C)C | ERα AF-2 | [5] |
| 168 | CC(C)CNc1cc(nc(n1)NCC(C)C)NCc2ccccc2 | ERα AF-2 | [5] |
| 169 | CC(C)CCc1cc(NCC(C)C)nc(n1)N(C)CC(C)C | ERα AF-2 | [5] |
| 170 | CC(C)CNc(n1)nc(N(C)CC(C)C)cc1CCc2cccc(c23)cccc3 | ERα AF-2 | [5] |
| 171 | CC(C)CNc(n1)nc(N(C)CC(C)C)cc1CCc2ccccc2 | ERα AF-2 | [5] |
| 172 | CC(C)CCc1cc(NCC(C)C)nc(n1)NCC(C)C | ERα AF-2 | [16] |
| 173 | CCCCc1cc(NCCC)nc(n1)NCCC | ERα AF-2 | [16] |
| 174 | c1ccccc1CCC2=CC(NCc3ccccc3)=NC(N2)NCc4ccccc4 | ERα AF-2 | [16] |
| 175 | Clc1c(Cl)ccc(c1)N(CC2)CCN2C(=O)CCCn(c3=O)c(=S)[nH]c(c34)cccc4 | ERα AF-2 | [17] |
| 176 | c1cccc(O)c1N(CC2)CCN2C(=O)CCCn(c3=O)c(=S)[nH]c(c34)cccc4 | ERα AF-2 | [17] |
| 177 | CC(C)NC(=O)CSc(n1)sc(c12)cc(cc2)NC(=O)CSc3cc(Cl)ccc3 | ERα AF-2 | [17] |
| 178 | NC(N)=[NH+]\N=C\C(=C1Cl)CCc(c12)cccc2 | ERα AF-2 | [18] |
| 179 | NC(N)=[NH+]\N=C\C(=C1Cl)CCc(c12)ccc(c2)OC | ERα AF-2 | [18] |
| 180 | NC(N)=[NH+]\N=C\C(=C1Cl)CCc(c12)cc(cc2)OC | ERα AF-2 | [18] |
| 181 | NC(N)=[NH+]\N=C\C(=C1Cl)CCc(c12)c(C)cc(C)c2 | ERα AF-2 | [18] |
| 182 | NC(N)=[NH+]\N=C\C(=C1Cl)C[C@@H](C)c(c12)cccc2 | ERα AF-2 | [18] |
| 183 | NC(N)=[NH+]\N=C\C(=C1Cl)Cc(c12)cccc2 | ERα AF-2 | [18] |
| 184 | NC(N)=[NH+]\N=C\C(=C1Cl)CCCc(c12)cccc2 | ERα AF-2 | [18] |
| 185 | NC(N)=[NH+]\N=C\C(=C1Br)CCc(c12)cccc2 | ERα AF-2 | [18] |
| 186 | c1cccc(c12)CCC(/C=N/[NH+]=C(N)N)=C2Oc3ccccc3 | ERα AF-2 | [18] |
| 187 | NC(N)=[NH+]\N=C\C=C(Cl)\c1ccccc1 | ERα AF-2 | [18] |
| 188 | NC(N)=[NH+]/N=C/C(C)=C(Cl)/c1ccccc1 | ERα AF-2 | [18] |
| 189 | NC(N)=[NH+]\N=C\c1cccc(c12)cccc2 | ERα AF-2 | [18] |
| 190 | NC(N)=[NH+]\N=C\c(c1)ccc(c12)cccc2 | ERα AF-2 | [18] |
| 191 | CC[C@@H](C)c1c(OCC([O-])=O)ccc(c1)-c(c2)ccc(c2[C@@H](C)CC)OCC[NH+](C)C | ERα AF-2 | [19] |
| 192 | CC[C@@H](C)c1c(OCC([O-])=O)ccc(c1)-c(c2)ccc(c2[C@H](C)CC)OCC[NH+](C)C | ERα AF-2 | [19] |
| 193 | CC[C@H](C)c1c(OCC([O-])=O)ccc(c1)-c(c2)ccc(c2[C@@H](C)CC)OCC[NH+](C)C | ERα AF-2 | [19] |
| 194 | CC[C@H](C)c1c(OCC([O-])=O)ccc(c1)-c(c2)ccc(c2[C@H](C)CC)OCC[NH+](C)C | ERα AF-2 | [19] |
| 195 | NC(N)=[NH+]\N=C\C(=C1Cl)CCc(c12)cccc2 | ERα AF-2 | [20] |
| 196 | C[NH+](C)CCOC(=O)Nc(cc1)ccc1Cc2ccc(cc2)NC(=O)OCC[NH+](C)C | ERα AF-2 | [20] |
| 197 | c1ccccc1C(\CC)=C(c2ccc(O)cc2)/c3ccc(cc3)OCC[NH+](C)C | ERβ AF-2 | [21] |
| 198 | c1ccccc1/C=C/c2cc(NCC(C)C)nc(n2)NCC(C)C | ERβ AF-2 | [5] |
| 199 | c1ccccc1CN(C(=O)OC(C)(C)C)c(nc(n2)NCC(C)C)cc2\C=C\c3ccccc3 | ERβ AF-2 | [5] |
| 200 | C=CC(=O)c1ccc(cc1)CCCCCC | TRα AF-2 | [22] |
| 201 | CCCCCCc(cc1)ccc1C(=O)CC[N@H+](C)CCc2ccccc2 | TRα AF-2 | [23] |

| | | | |
|---|---|---|---|
| 202 | CCCCCCc(cc1)ccc1C(=O)CC[N@H+](C)CCc2ccccc2 | TRα AF-2 | [23] |
| 203 | CC(C)[NH+](C(C)C)CCC(=O)c1ccc(cc1)CCCCCC | TRα AF-2 | [23] |
| 204 | C1CC=CN1CCC(=O)c2ccc(cc2)CCCCCC | TRα AF-2 | [23] |
| 205 | C1COCCN1CCC(=O)c2ccc(cc2)CCCCCC | TRα AF-2 | [23] |
| 206 | CCCC[NH+](CCCC)CCC(=O)c1ccc(cc1)CCCCCC | TRα AF-2 | [23] |
| 207 | C[NH+](C)CCC(=O)c1ccc(cc1)CCCCCC | TRα AF-2 | [23] |
| 208 | C1CCCCC1[NH+](C2CCCCC2)CCC(=O)c3ccc(cc3)CCCCCC | TRα AF-2 | [23] |
| 209 | CCC[NH2+]CCC(=O)c1ccc(cc1)CCCCCC | TRα AF-2 | [23] |
| 210 | [O-]C(=O)/C=C\C(=O)c1ccc(cc1)CCCCCC | TRα AF-2 | [23] |
| 211 | C\C=C\C(=O)c1ccc(cc1)CCCCCCC | TRα AF-2 | [23] |
| 212 | C=C(C)C(=O)c1ccc(cc1)CCCCCCC | TRα AF-2 | [23] |
| 213 | C=CC(=O)c1ccc(cc1)CCCC | TRα AF-2 | [23] |
| 214 | C=CC(=O)c1ccc(cc1)CCCCC | TRα AF-2 | [23] |
| 215 | C=CC(=O)c1ccc(cc1)CC(C)(C)C | TRα AF-2 | [23] |
| 216 | C=CC(=O)c1ccc(cc1)CCCCCCC | TRα AF-2 | [23] |
| 217 | C=CC(=O)c1ccc(cc1)CCCCCCCC | TRα AF-2 | [23] |
| 218 | C=CC(=O)[C@H]1CC[C@@H](CC1)CC(C)(C)C | TRα AF-2 | [23] |
| 219 | C=CC(=O)OC(=O)c1c(cccc1)CCCCCC | TRα AF-2 | [23] |
| 220 | C=CC(=O)Nc(cc1)ccc1CCCCCC | TRα AF-2 | [23] |
| 221 | [O-]C(=O)/C=C\C(=O)Nc(cc1)ccc1CCCCCC | TRα AF-2 | [23] |
| 222 | C\C=C\C(=O)Nc(cc1)ccc1CCCCCC | TRα AF-2 | [23] |
| 223 | C#CC(=O)Nc(cc1)ccc1CCCCCC | TRα AF-2 | [23] |
| 224 | C#CC(=O)Oc(cc1)ccc1CCCCCC | TRα AF-2 | [23] |
| 225 | ClCC(=O)c1ccc(cc1)CCCCCC | TRα AF-2 | [23] |
| 226 | BrCCC(=O)c1ccc(cc1)CCCCCC | TRα AF-2 | [23] |
| 227 | O1C[C@@H]1C(=O)c2ccc(cc2)CCCCCC | TRα AF-2 | [23] |
| 228 | C=CC(=O)c1ccc(cc1)CCCCCC | TRβ AF-2 | [22] |
| 229 | CCCCCCc(cc1)ccc1C(=O)CC[N@H+](C)CCc2ccccc2 | TRβ AF-2 | [23] |
| 230 | CCCCCCc1ccc(C(=O)CCN(C)CCC)cc1 | TRβ AF-2 | [23] |
| 231 | CC(C)[NH+](C(C)C)CCC(=O)c1ccc(cc1)CCCCCC | TRβ AF-2 | [23] |
| 232 | C1CC=CN1CCC(=O)c2ccc(cc2)CCCCCC | TRβ AF-2 | [23] |
| 233 | C1COCCN1CCC(=O)c2ccc(cc2)CCCCCC | TRβ AF-2 | [23] |
| 234 | CCCC[NH+](CCCC)CCC(=O)c1ccc(cc1)CCCCCC | TRβ AF-2 | [23] |
| 235 | C[NH+](C)CCC(=O)c1ccc(cc1)CCCCCC | TRβ AF-2 | [23] |
| 236 | C1CCCCC1[NH+](C2CCCCC2)CCC(=O)c3ccc(cc3)CCCCCC | TRβ AF-2 | [23] |
| 237 | CCC[NH2+]CCC(=O)c1ccc(cc1)CCCCCC | TRβ AF-2 | [23] |
| 238 | [O-]C(=O)/C=C\C(=O)c1ccc(cc1)CCCCCC | TRβ AF-2 | [23] |
| 239 | C\C=C\C(=O)c1ccc(cc1)CCCCCCC | TRβ AF-2 | [23] |
| 240 | C=C(C)C(=O)c1ccc(cc1)CCCCCCC | TRβ AF-2 | [23] |
| 241 | C=CC(=O)c1ccc(cc1)CCC | TRβ AF-2 | [23] |
| 242 | C=CC(=O)c1ccc(cc1)CCCC | TRβ AF-2 | [23] |
| 243 | C=CC(=O)c1ccc(cc1)CCCCC | TRβ AF-2 | [23] |
| 244 | C=CC(=O)c1ccc(cc1)CC(C)(C)C | TRβ AF-2 | [23] |
| 245 | C=CC(=O)c1ccc(cc1)CCCCCCC | TRβ AF-2 | [23] |
| 246 | C=CC(=O)c1ccc(cc1)CCCCCCCC | TRβ AF-2 | [23] |
| 247 | C=CC(=O)[C@H]1CC[C@@H](CC1)CC(C)(C)C | TRβ AF-2 | [23] |
| 248 | C=CC(=O)OC(=O)c1ccc(cc1)CCC | TRβ AF-2 | [23] |
| 249 | C=CC(=O)OC(=O)c1ccc(cc1)CCCCC | TRβ AF-2 | [23] |
| 250 | C=CC(=O)OC(=O)c1c(cccc1)CCCCCC | TRβ AF-2 | [23] |
| 251 | C=CC(=O)c1ccc(cc1)NC(=O)CCC | TRβ AF-2 | [23] |
| 252 | C=CC(=O)c(c1)ccc(c12)CCCC2 | TRβ AF-2 | [23] |

| | | | |
|---|---|---|---|
| 253 | C=CC(=O)Nc(cc1)ccc1CCCCCC | TRβ AF-2 | [23] |
| 254 | [O-]C(=O)/C=C\C(=O)Nc(cc1)ccc1CCCCCC | TRβ AF-2 | [23] |
| 255 | C\C=C\C(=O)Nc(cc1)ccc1CCCCCC | TRβ AF-2 | [23] |
| 256 | C#CC(=O)Nc(cc1)ccc1CCCCCC | TRβ AF-2 | [23] |
| 257 | C#CC(=O)Oc(cc1)ccc1CCCCCC | TRβ AF-2 | [23] |
| 258 | ClCC(=O)c1ccc(cc1)CCCCCC | TRβ AF-2 | [23] |
| 259 | BrCCC(=O)c1ccc(cc1)CCCCCC | TRβ AF-2 | [23] |
| 260 | O1C[C@@H]1C(=O)c2ccc(cc2)CCCCCC | TRβ AF-2 | [23] |
| 261 | C[NH+](C)CCC(=O)c1ccc(cc1)OCCCCCC | TRβ AF-2 | [24] |
| 262 | C[NH+](C)CCC(=O)c1cc(ccc1)OCCCCCC | TRβ AF-2 | [24] |
| 263 | C[NH+](C)CCC(=O)c1ccc(c(c12)cccc2)OCCCCCC | TRβ AF-2 | [24] |
| 264 | CCCCCCOc(cc1)cc(c12)C[C@H](C2=O)C[NH+](C)C | TRβ AF-2 | [24] |
| 265 | CCCCCCOc(cc1)cc(c12)C[C@@H](C2=O)C[NH+](C)C | TRβ AF-2 | [24] |
| 266 | CCCCCCOc(cc1)cc(c12)CC[C@@H](C2=O)C[NH+](C)C | TRβ AF-2 | [24] |
| 267 | CCCCCCOc(cc1)cc(c12)CC[C@H](C2=O)C[NH+](C)C | TRβ AF-2 | [24] |
| 268 | CCCCCCOc(cc1)cc(c12)OC[C@@H](C2=O)C[NH+](C)C | TRβ AF-2 | [24] |
| 269 | CCCCCCOc(cc1)cc(c12)OC[C@@H](C2=O)CN(C)C | TRβ AF-2 | [24] |
| 270 | CCCC[NH+](CCCC)CCC(=O)c1ccc(cc1)OCCCCCC | TRβ AF-2 | [24] |
| 271 | C1CCCC[NH+]1CCC(=O)c2ccc(cc2)OCCCCCC | TRβ AF-2 | [24] |
| 272 | C1CCC[NH+]1CCC(=O)c2ccc(cc2)OCCCCCC | TRβ AF-2 | [24] |
| 273 | C[C@@H]1C[N@H+]1CCC(=O)c2ccc(cc2)OCCCCCC | TRβ AF-2 | [24] |
| 274 | C1CN(C)CCN1CCC(=O)c2ccc(cc2)OCCCCCC | TRβ AF-2 | [24] |
| 275 | C1CN(C)CCN1CCC(=O)c2ccc(cc2)OCCCCCC | TRβ AF-2 | [24] |
| 276 | CCCCCCOc(cc1)ccc1C(=O)CCN2CCN(CC2)c3ccccc3 | TRβ AF-2 | [24] |
| 277 | CCCCCCOc(cc1)ccc1C(=O)CC[NH+](CC2)CCN2c3ccccc3 | TRβ AF-2 | [24] |
| 278 | C1COCCN1CCC(=O)c2ccc(cc2)OCCCCCC | TRβ AF-2 | [24] |
| 279 | C[NH+](C)CCC(=O)c1ccc(cc1)SCCCCCC | TRβ AF-2 | [24] |
| 280 | C[NH+](C)CCC(=O)c1ccc(cc1)S(=O)(=O)CCCCCC | TRβ AF-2 | [24] |
| 281 | C[NH+](C)CCC(=O)c1ccc(cc1)C(=O)NCCCCCC | TRβ AF-2 | [24] |
| 282 | C[NH+](C)CCC(=O)c1ccc(cc1)NC(=O)CCCCC | TRβ AF-2 | [24] |
| 283 | CCCCCCS(=O)(=O)c2ccc(C(=O)CCN1CCNC(=O)C1)c(Cl)c2Cl | TRβ AF-2 | [24] |
| 284 | CCCCCCS(=O)(=O)c2ccc(C(=O)CCN1CCN(C(C)=O)C(=O)C1)c(Cl)c2Cl | TRβ AF-2 | [24] |
| 285 | CCCCCCS(=O)(=O)c2cc(Cl)c(C(=O)CCN1CCNC(=O)C1)cc2Cl | TRβ AF-2 | [24] |
| 286 | CCCCCCS(=O)(=O)c2cc(Cl)c(C(=O)CCN1CCN(C(C)=O)C(=O)C1)cc2Cl | TRβ AF-2 | [24] |
| 287 | C1[C@H](C2)C[C@@H](C3)C[C@H]2CC13NC(=O)COC(=O)c4cc([N+]([O-])=O)c(cc4)S(=O)(=O)C | TRβ AF-2 | [25] |
| 288 | C1CCCCC1C(=O)NC(=O)COC(=O)c2cc([N+]([O-])=O)c(cc2)S(=O)(=O)C | TRβ AF-2 | [25] |
| 289 | CN3CC[C@]2(C)c1ccccc1[N@](C)C2O3 | TRβ AF-2 | [25] |
| 290 | C1CCCCC1NC(=O)NC(=O)COC(=O)c2cc([N+]([O-])=O)c(cc2)S(=O)(=O)C | TRβ AF-2 | [26] |
| 291 | Cn1cccc1C(=O)NC(=O)COC(=O)c2cc([N+]([O-])=O)c(cc2)S(=O)(=O)C | TRβ AF-2 | [26] |
| 292 | C[C@@]12C(C)(C)[C@H](CC2)[C@@H](C1)NC(=O)COC(=O)c3cc([N+]([O-])=O)c(cc3)S(=O)(=O)C | TRβ AF-2 | [26] |
| 293 | CC1CCN(CC1)C(=O)[C@H](C)OC(=O)c2cc([N+]([O-])=O)c(cc2)S(=O)(=O)C | TRβ AF-2 | [26] |
| 294 | CC1CCN(CC1)C(=O)[C@@H](C)OC(=O)c2cc([N+]([O-])=O)c(cc2)S(=O)(=O)C | TRβ AF-2 | [26] |
| 295 | C[C@@H]1CCCCN1C(=O)COC(=O)c2cc([N+]([O-])=O)c(cc2)S(=O)(=O)C | TRβ AF-2 | [26] |
| 296 | C[C@H]1CCCCN1C(=O)COC(=O)c2cc([N+]([O-])=O)c(cc2)S(=O)(=O)C | TRβ AF-2 | [26] |
| 297 | C1CCCN1C(=O)COC(=O)c2cc([N+]([O-])=O)c(cc2)S(=O)(=O)C | TRβ AF-2 | [26] |
| 298 | c1cccc(c12)NC(=O)CN2C(=O)COC(=O)c3cc([N+]([O-])=O)c(cc3)S(=O)(=O)C | TRβ AF-2 | [26] |
| 299 | c1cccc(c12)N(CC2)C(=O)COC(=O)c3cc([N+]([O-])=O)c(cc3)S(=O)(=O)C | TRβ AF-2 | [26] |
| 300 | CC(=O)c1cc(ccc1)NC(=O)[C@H](C)OC(=O)c2cc([N+]([O-])=O)c(cc2)S(=O)(=O)C | TRβ AF-2 | [26] |
| 301 | CC(=O)c1cc(ccc1)NC(=O)[C@@H](C)OC(=O)c2cc([N+]([O-])=O)c(cc2)S(=O)(=O)C | TRβ AF-2 | [26] |
| 302 | C1[C@@H](C2)C[C@H](C3)C[C@@H]2[C@H]([C@@H]13)NC(=O)COC(=O)c4cc([N+]([O-])=O)c(cc4)S(=O)(=O)C | TRβ AF-2 | [26] |
| 303 | C1[C@@H](C2)C[C@H](C3)C[C@@H]2[C@H]([C@@H]13)NC(=O)COC(=O)c4cc([N+]([O-])=O)c(F)cc4 | TRβ AF-2 | [26] |

| | | | |
|---|---|---|---|
| 304 | C1[C@H](C2)C[C@@H](C3)C[C@H]2CC13NC(=O)c4cnc(s4)-c5cc([N+]([O-])=O)c(cc5)S(=O)(=O)C | TRβ AF-2 | [27] |
| 305 | C1CCCCN1C(=O)c2cnc(s2)-c3cc([N+]([O-])=O)c(cc3)S(=O)(=O)C | TRβ AF-2 | [27] |
| 306 | C[C@@]12C[C@H](CC(C)(C)C2)N(C1)C(=O)c3c(C)nc(s3)-c4cc([N+]([O-])=O)c(cc4)S(=O)(=O)C | TRβ AF-2 | [27] |
| 307 | C1CCCCN1C(=O)c2c(C)nc(s2)-c3cc([N+]([O-])=O)c(cc3)S(=O)(=O)C | TRβ AF-2 | [27] |
| 308 | CC1CCN(CC1)C(=O)c2c(C)nc(s2)-c3cc([N+]([O-])=O)c(cc3)S(=O)(=O)C | TRβ AF-2 | [27] |
| 309 | C[C@]12C[C@@H](CC(C)(C)C2)N(C1)C(=O)c3c(CC)nc(s3)-c4cc([N+]([O-])=O)c(cc4)S(=O)(=O)C | TRβ AF-2 | [27] |
| 310 | C[C@@]12C[C@H](CC(C)(C)C2)N(C1)C(=O)c3c(CC)nc(s3)-c4cc([N+]([O-])=O)c(cc4)S(=O)(=O)C | TRβ AF-2 | [27] |
| 311 | C1CCCCN1C(=O)c2c(CC)nc(s2)-c3cc([N+]([O-])=O)c(cc3)S(=O)(=O)C | TRβ AF-2 | [27] |
| 312 | C[C@]12C[C@@H](CC(C)(C)C2)N(C1)C(=O)c(c3C(F)(F)F)sc(n3)-c4cc([N+]([O-])=O)c(cc4)S(=O)(=O)C | TRβ AF-2 | [27] |
| 313 | C[C@@]12C[C@H](CC(C)(C)C2)N(C1)C(=O)c(c3C(F)(F)F)sc(n3)-c4cc([N+]([O-])=O)c(cc4)S(=O)(=O)C | TRβ AF-2 | [27] |
| 314 | C1CCCCN1C(=O)c(c2C(F)(F)F)sc(n2)-c3cc([N+]([O-])=O)c(cc3)S(=O)(=O)C | TRβ AF-2 | [27] |
| 315 | CC1CCN(CC1)C(=O)c(c2C(F)(F)F)sc(n2)-c3cc([N+]([O-])=O)c(cc3)S(=O)(=O)C | TRβ AF-2 | [27] |
| 316 | c1cccc(c12)N([C@H](C)C2)C(=O)c(c3C(F)(F)F)sc(n3)-c4cc([N+]([O-])=O)c(cc4)S(=O)(=O)C | TRβ AF-2 | [27] |
| 317 | c1cccc(c12)N([C@@H](C)C2)C(=O)c(c3C(F)(F)F)sc(n3)-c4cc([N+]([O-])=O)c(cc4)S(=O)(=O)C | TRβ AF-2 | [27] |
| 318 | C1CCCCN1C(=O)c2c(-c3ccccc3)nc(s2)-c4cc([N+]([O-])=O)c(cc4)S(=O)(=O)C | TRβ AF-2 | [27] |
| 319 | c1ccc(F)cc1CN(C)C(=O)c2cnc(s2)-c3cc([N+]([O-])=O)c(cc3)S(=O)(=O)C | TRβ AF-2 | [27] |
| 320 | c1cccc(c12)CN(CC2)C(=O)c(c3C(F)(F)F)sc(n3)-c4cc([N+]([O-])=O)c(cc4)S(=O)(=O)C | TRβ AF-2 | [27] |
| 321 | c1ccccc1CN(C)C(=O)c(c2C(F)(F)F)sc(n2)-c3cc([N+]([O-])=O)c(cc3)S(=O)(=O)C | TRβ AF-2 | [27] |
| 322 | c1cccc(F)c1CN(C)C(=O)c(c2C(F)(F)F)sc(n2)-c3cc([N+]([O-])=O)c(cc3)S(=O)(=O)C | TRβ AF-2 | [27] |
| 323 | c1ccc(F)cc1CN(C)C(=O)c(c2C(F)(F)F)sc(n2)-c3cc([N+]([O-])=O)c(cc3)S(=O)(=O)C | TRβ AF-2 | [27] |
| 324 | c1ccccc1N(CCC)C(=O)c2csc(n2)-c3cc([N+]([O-])=O)c(cc3)S(=O)(=O)C | TRβ AF-2 | [27] |
| 325 | C=CC(=O)c1ccc(cc1)CCCCCC | TRβ AF-2 | [28] |
| 326 | CCC(=O)c1ccc(cc1)CCCCCC | TRβ AF-2 | [28] |
| 327 | [NH3+]Cc1ccc(cc1)-c(n2)cn3c2sc(c34)cccc4 | GR AF_2 | [29] |
| 328 | [NH3+]Cc1ccc(cc1)-c(n2)cn3c2sc(c34)CCCC4 | GR AF_2 | [29] |
| 329 | OCc1ccc(cc1)-c(n2)cn3c2sc(c34)cccc4 | GR AF_2 | [29] |
| 330 | Cc1ccc(cc1)-c(n2)cn3c2sc(c34)cccc4 | GR AF_2 | [29] |
| 331 | N#Cc1ccc(cc1)-c(c2)nc(n3CC)n2c(c34)cccc4 | GR AF_2 | [29] |
| 332 | c1cccc(c12)sc3n2cc(n3)-c4ccc(N)cc4 | GR AF_2 | [29] |
| 333 | c1cccc(c12)sc3n2cc(n3)-c4ccc(Br)cc4 | GR AF_2 | [29] |
| 334 | N#Cc1ccc(cc1)-c(n2)cn3c2sc(c34)CCCC4 | GR AF_2 | [29] |

[a]SMILES code exported from Maestro.
[b]Reference order in supporting information.

### Protein Preparation

**Table S21.** Protein structures used in this study.

| Receptor | Crystal structures MD | Crystal structures Docking | Template structures | UniProt entry |
|---|---|---|---|---|
| AR | 3L3X | 2PIT | n/a | P10275 |
| ERα | 5WGD | 3UUD | 1X7R | P03372 |
| ERβ | 4J24 | 2J7Y | 3OLS | Q92731 |
| GR | 5NFP | 3K22 | n/a | P04150 |
| MR | 2AA2 | 2AA2 | 2A3I | P08235 |
| PR | 1A28 | 1A28 | n/a | P06401 |
| TRα | 4LNW | 4LNW | n/a | P10827 |
| TRβ | 1XZX | 3GWS | 2J4A | P10828 |

[a]Structures that were used to complete missing loops. For several receptors, no additional structures were used.

### MD Simulations

**Table S22.** Conventional Desmond relaxation protocol.

| Desmond stage | Procedure |
|---|---|
| 1 | Task (reading files, initializing parameters) |
| 2 | Simulate, Brownian Dynamics, NVT, T = 10 K, small time steps, and restraints on solute heavy atoms, 100 ps |
| 3 | Simulate, NVT, T = 10 K, small time steps, and restraints on solute heavy atoms, 12 ps |
| 4 | Simulate, NPT, T = 10 K, and restraints on solute heavy atoms, 12 ps |
| 5 | Solvate pocket |
| 6 | Simulate, NPT and restraints on solute heavy atoms, 12 ps |
| 7 | Simulate, NPT and no restraints, 24 ps |

The information about this default relaxation protocol was adapted from our previous work[1].

**Table S23.** Mixed Solvent MD Desmond relaxation protocol.

| Desmond stage | Procedure |
|---|---|
| 1 | Brownian Dynamics, NVT, T = 10 K, 1 fs timestep, and restraints on all solute atoms, 24 ps |
| 2 | Brownian Dynamics, NVT, T = 10 K, 1 fs timestep, and restraints on solute heavy atoms, 24 ps |
| 3 | NVT, T = 10 K, 1 fs timestep, restraints on solute heavy atoms, 12 ps |
| 4 | NPT, T = 10 K, 2 fs timestep, restraints on solute heavy atoms, 12 ps |
| 5 | NPT, T= 300 K, 2 fs timestep, restraints on solute heavy atoms, 24 ps |
| 6 | NPT, T = 300 K, 2 fs timestep, 15 ps |

The information about this default relaxation protocol was retrieved from the program documentation.

### Crystal Structure Analysis

**Table S24.** Number input structures and minimal amount for cluster to be considered as conserved.

| Receptor | Number of input structures | Minimal occupancy |
|---|---|---|
| AR | 67 | 7 |
| ERα | 229 | 23 |
| ERβ | 32 | 3 |
| GR | 20 | 2 |
| MR | 27 | 3 |
| PR | 16 | 2 |
| TRα | 8 | 1 |
| TRβ | 9 | 1 |

## References


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