## Supplementary Information

# Conformational Dynamics of Androgen Receptors Bound to Agonists and Antagonists

Hyo Jin Gim[†], Jiyong Park[†], Michael E. Jung[*] and K. N. Houk[*]

Department of Chemistry and Biochemistry, University of California, Los Angeles, Los Angeles, California 90095-1569

jung@chem.ucla.edu Tel 310-825-7954

houk@chem.ucla.edu Tel 310-206-0515

[†] These authors contributed equally to this work

# Table of Contents

# Supplementary Figures

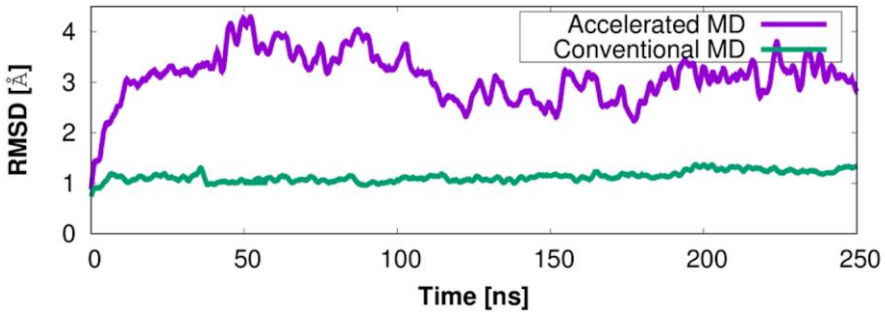



**Figure S1**. Comparison of the backbone RMSDs of the wild type AR bound to ENZ in *conformation 2*: conventional MD and accelerated MD simulations.

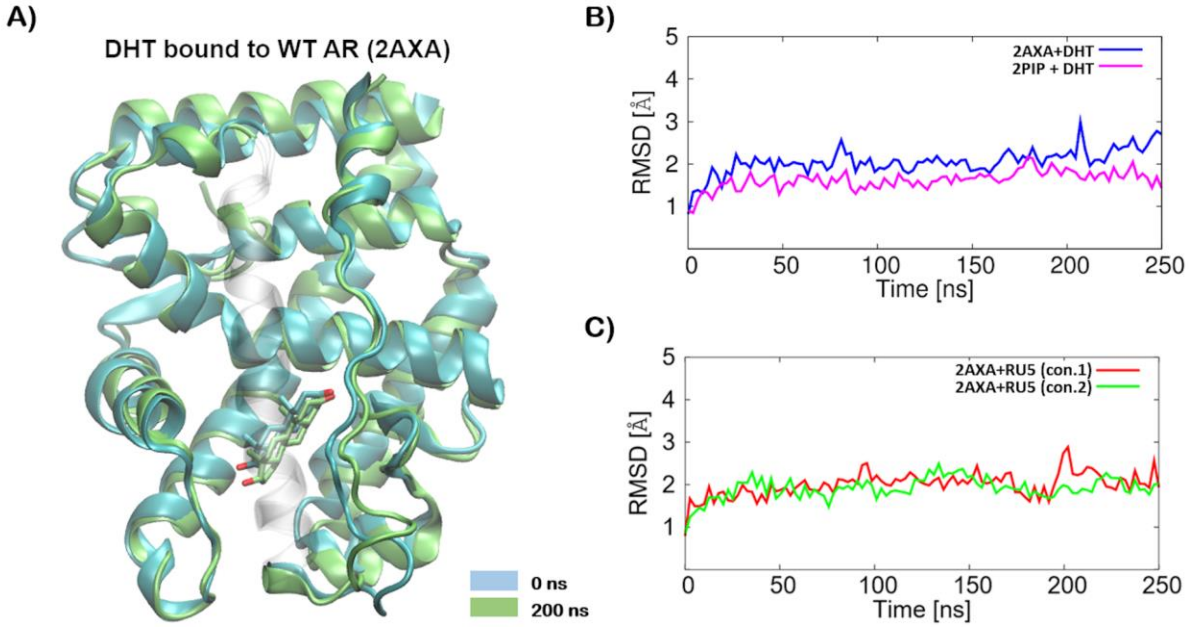



**Figure S2**. (A) The snapshots of DHT bound to the wild type AR of the initial structure (PDB ID: 2AXA) and aMD trajectories after 200 ns simulation. (B) The backbone RMSDs of the wild type ARs bound to DHT and (C) RU5 during 250 simulations.

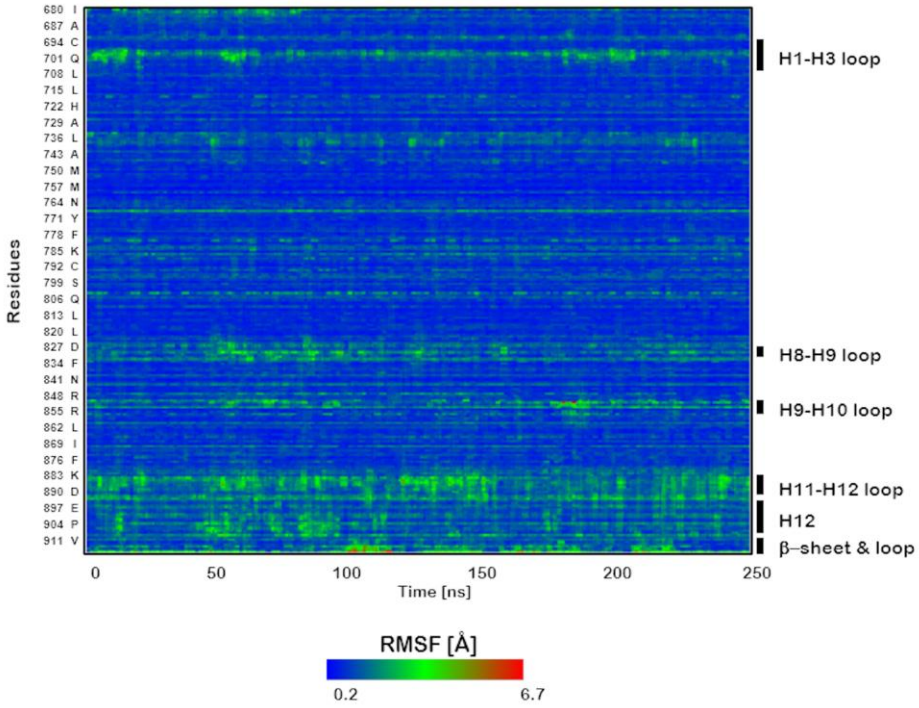



**Figure S3**. Cα RMSF over the time of the wild type AR bound to ENZ in *conformation 2*.

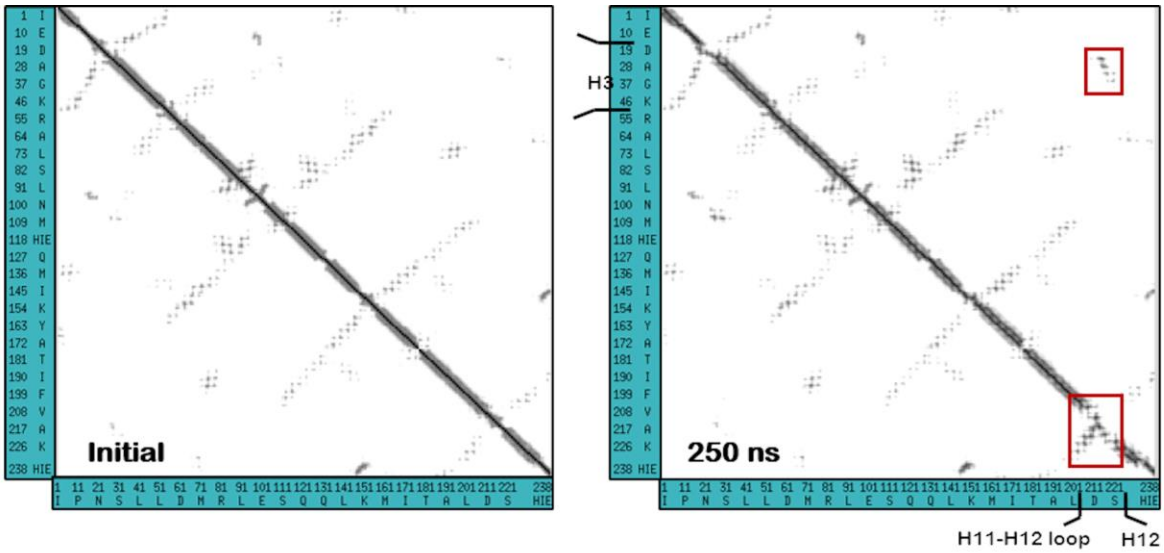



**Figure S4**. Cα to Cα distance of each residue pair in the initial (PDB ID: 2XAX) and simulated structures of the wild type AR bound to ENZ in *conformation 2.* A graph square is colored black at 0 Å, to a linear gray scale between 0 and 10 Å, and white when equal to or greater than 10 Å.

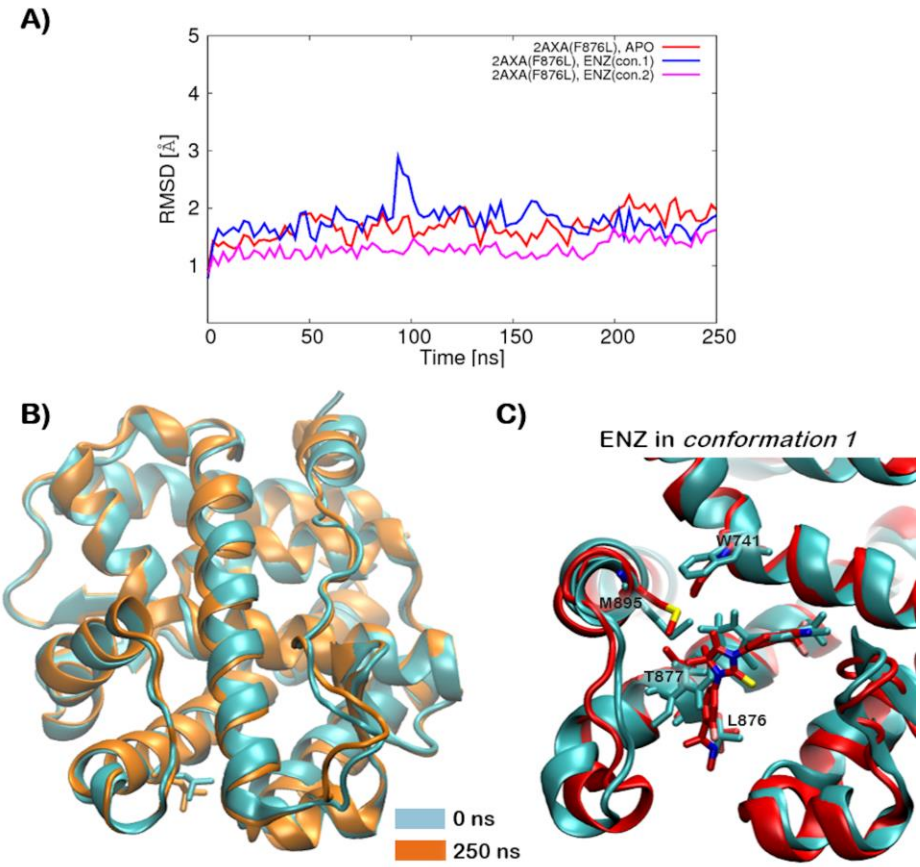



**Figure S5**. (A) The backbone RMSDs of the F876L mutant ARs bound to ENZ in *conformation 1, 2* and in the absence of the ligand. (B) A superimposed snapshot of the initial and 250 ns simulated structures of *apo* F876L mutant ARs. (C) The snapshot of F876L mutant AR bound to ENZ in *conformation 1*. The initial structures of F876L mutant ARs are colored in cyan and the simulated structures are colored in orange (*apo*) and red (ENZ in *conformation 1*), respectively.

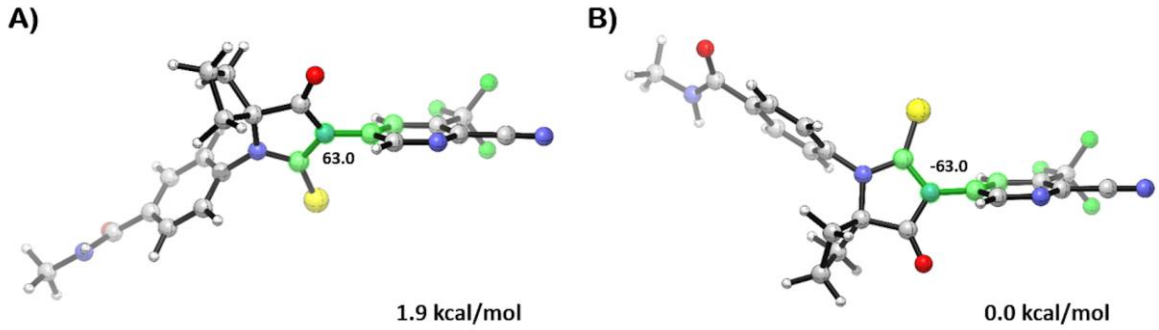



**Figure S6.** Two conformers of APL with the lowest energy. (A) Conformer with the second lowest energy (*conformation 1*) and (B) the other conformer with the lowest in energy conformation (*conformation 2*). The dihedral angles of the four highlighted atoms (C-C-N-C) are shown..

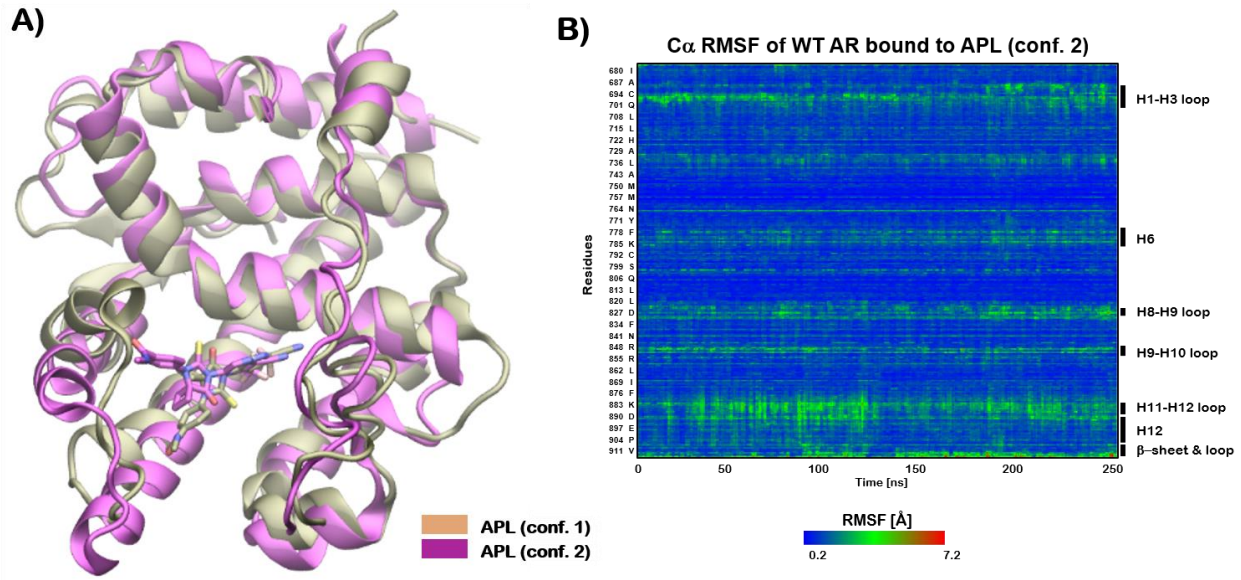



**Figure S7**. (A) The comparison of the wild type ARs bound to APL in *conformation1* and *conformations 2* after 250 ns aMD simulations. (B) Cα RMSF over the time during 250 ns aMD simulations (PDB ID: 2AXA).

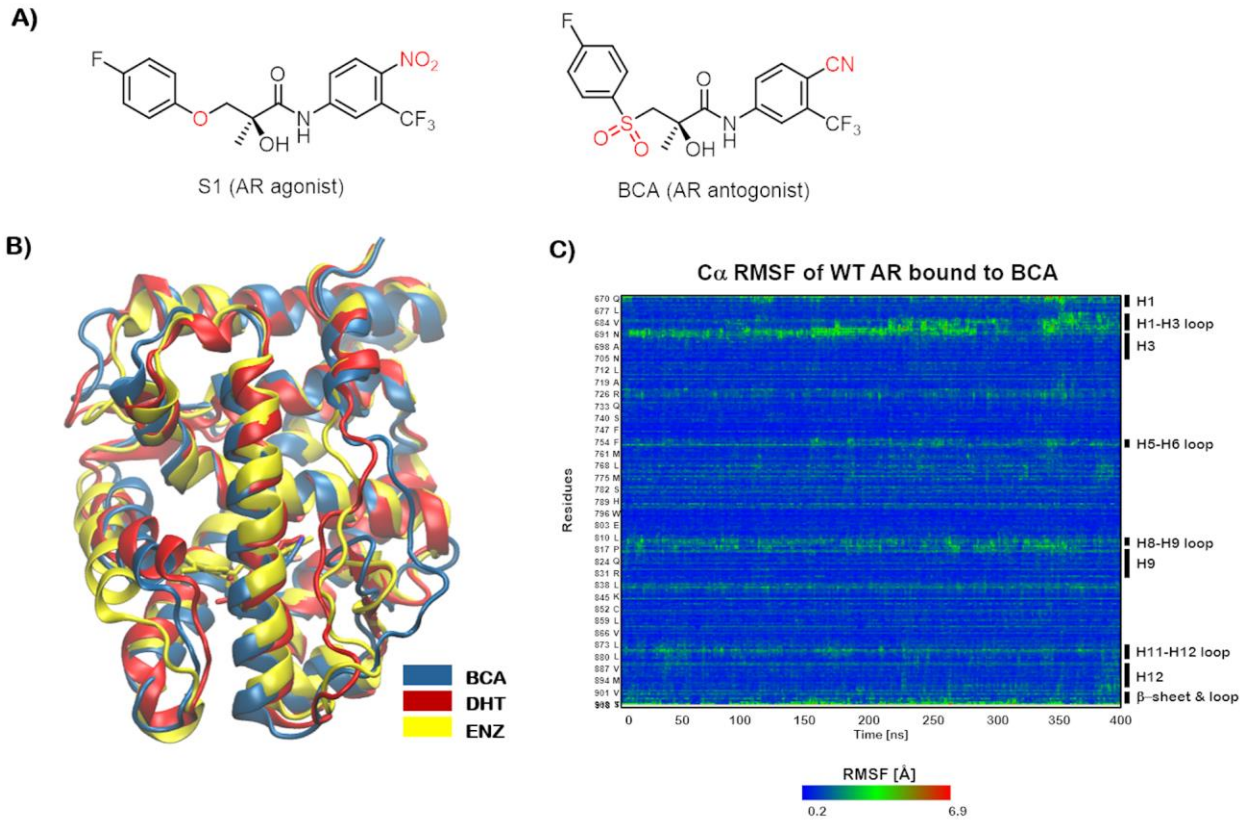



**Figure S8**. (A) Chemical structures of originally crystalized ligand S1 and BCA. (B) Comparison of the wild type ARs bound to BCA, DHT and ENZ after 250 ns aMD simulations. (C) Cα RMSF over the time during 400 ns aMD simulations (PDB ID: 2PIP).

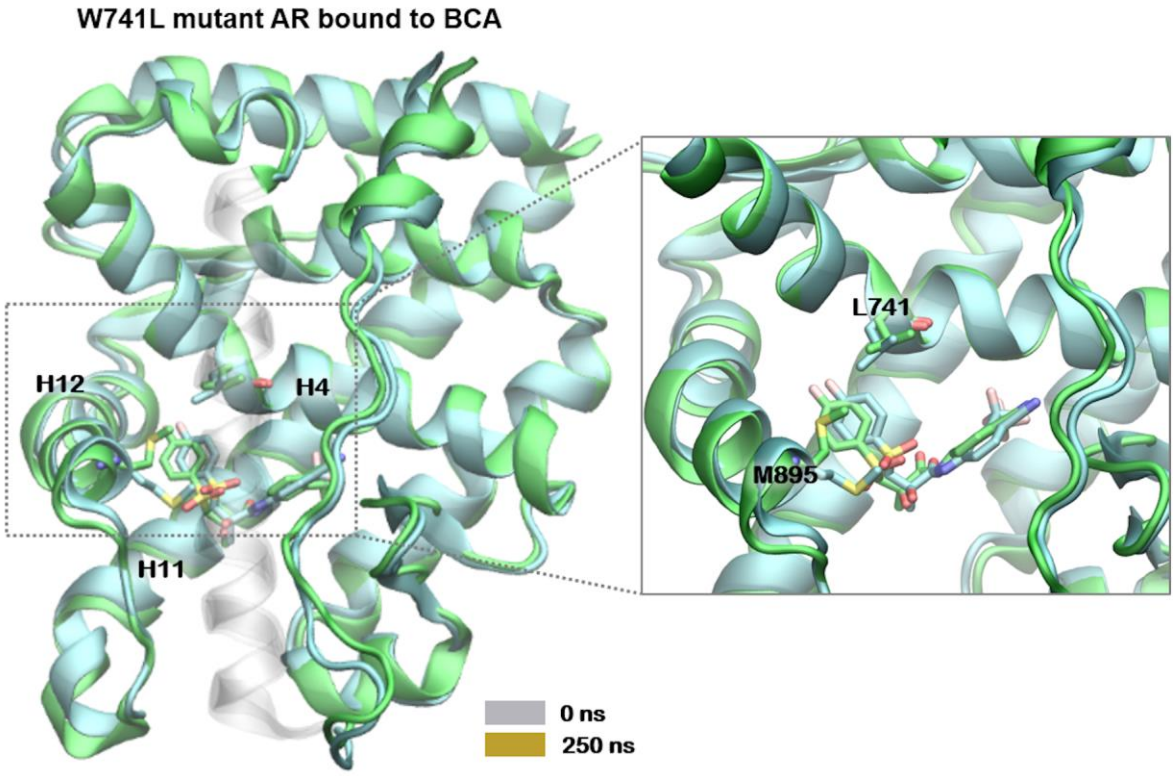



**Figure S9**. Comparison of W741L mutant ARs bound to BCA in *conformation 2* at 0 ns and 250 ns.

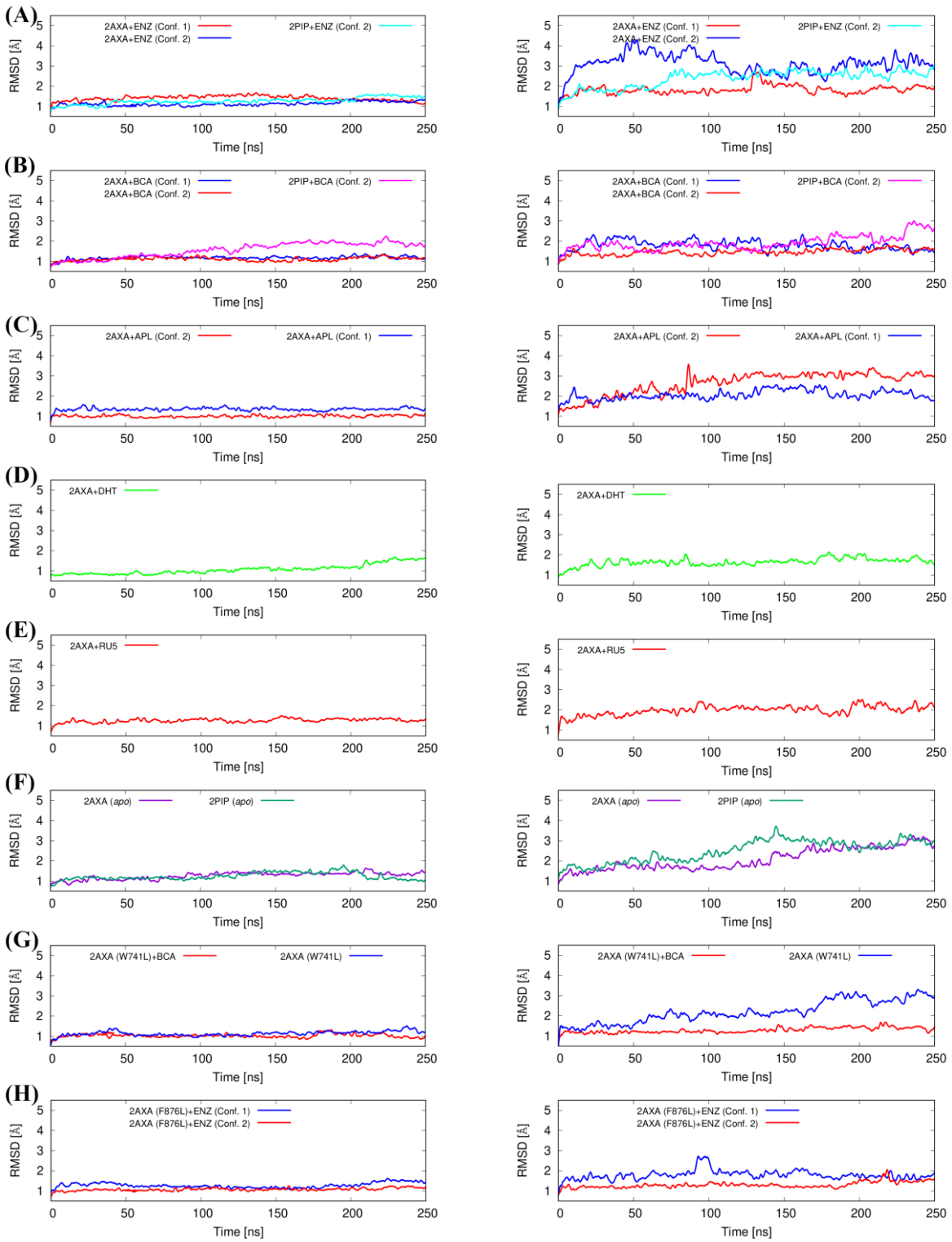



**Figure S10**. The backbone RMSDs of conventional MD simulations (left column) and aMD simulations (right column). (A) wild type ARs bound to ENZ (B) wild type ARs bound to BCA (C) wild type ARs bound to APL (D) wild type AR bound to DHT (E) wild type AR bound to RU5 (F) wild type ARs in apo (G) W741 mutant ARs bound to BCA (H) F876L mutant ARs bound to ENZ.

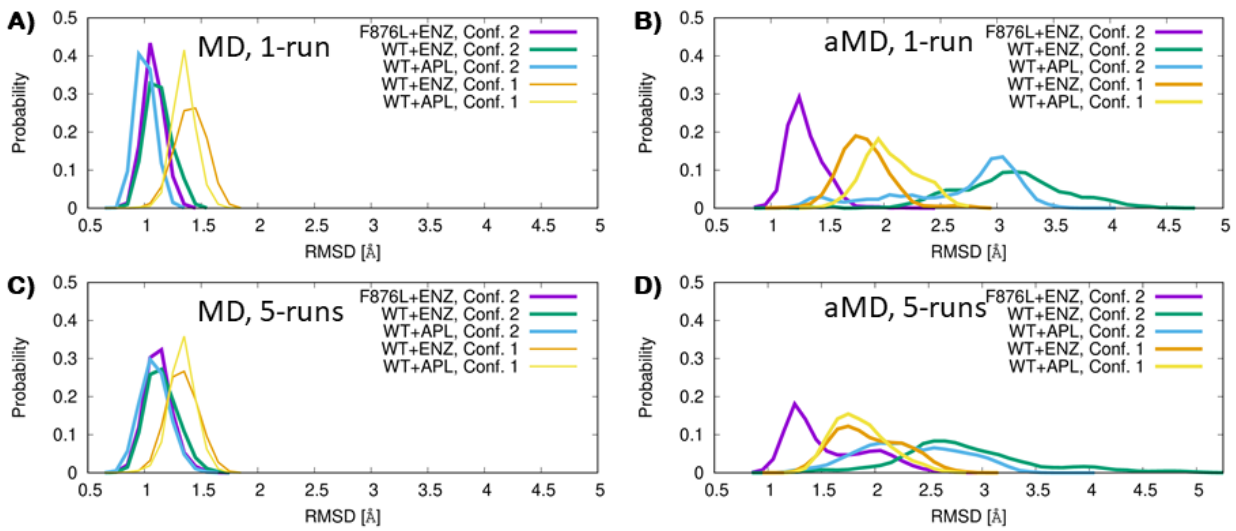



**Figure S11**. Comparison of the backbone RMSD sampled from single and multiple copies of MD and aMD simulations: probability density of RMSDs sampled from (A) single and (C) 5-copies of conventional MD; probability density of RMSDs sampled from (B) single and (D) 5-copies of accelerated MD simulations.

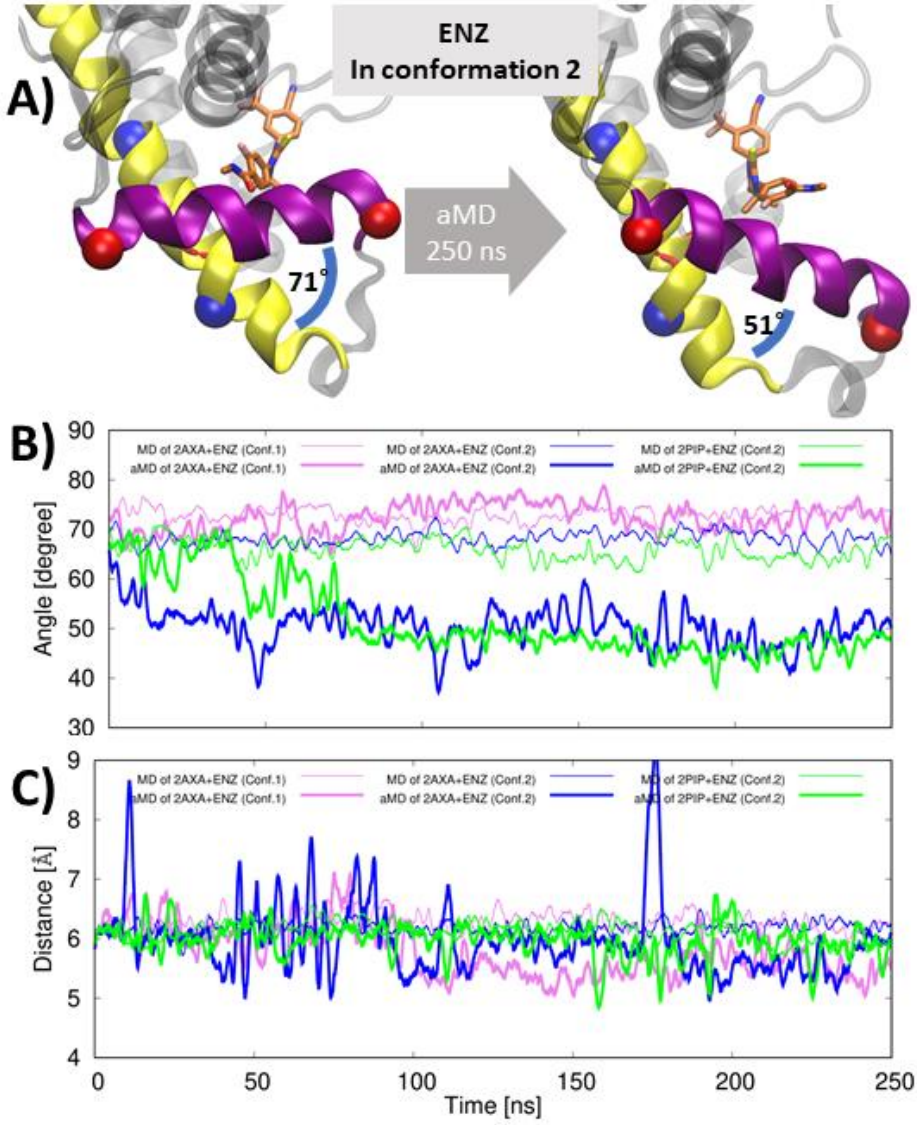



**Figure S12**. Conformational changes of the helix 11 (H11) in AR bound to enzalutamide, observed from the MD and the aMD simulations: (A) comparison of the H11 in the initial and the last (250 ns) conformation sampled from aMD simulation; (B) relative angles and (C) minimal distance between H11 and H12 observed from the MD and the aMD simulations.

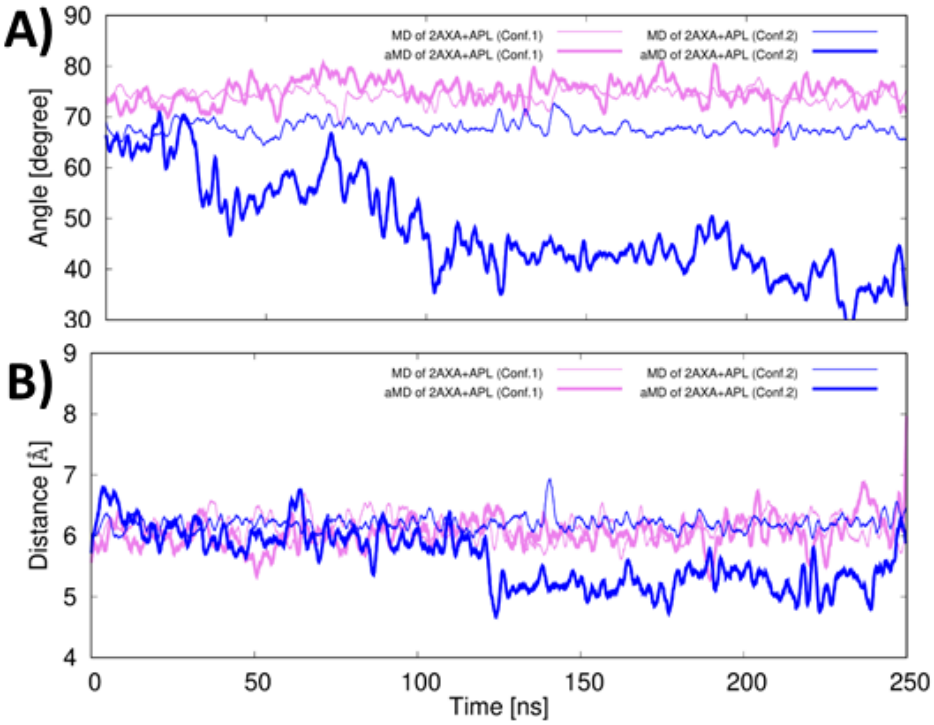
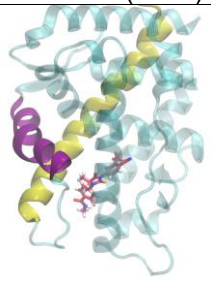
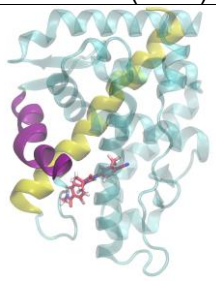
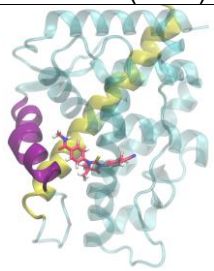
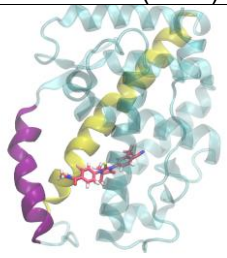
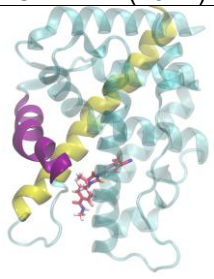
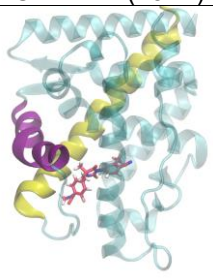
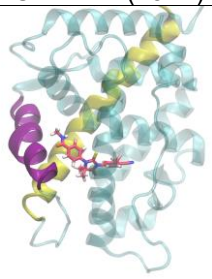
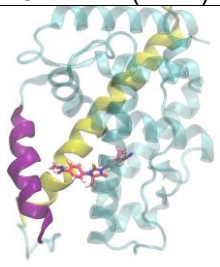
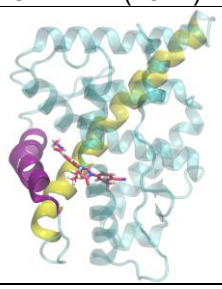
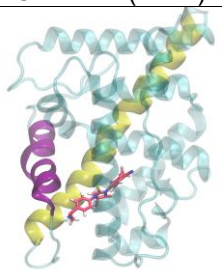
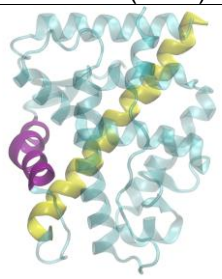
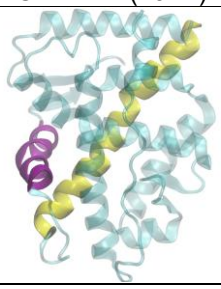
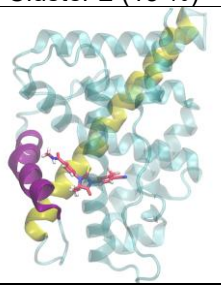
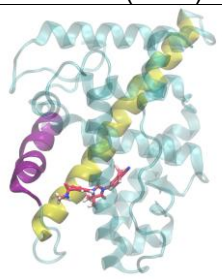
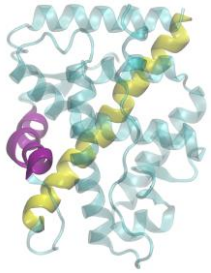
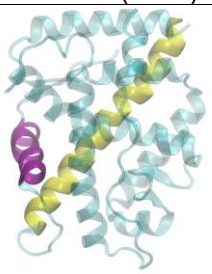
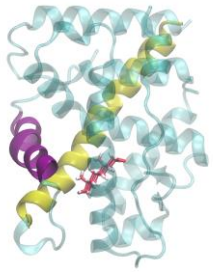
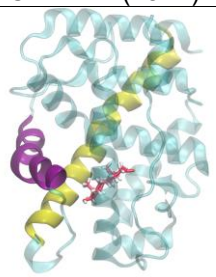
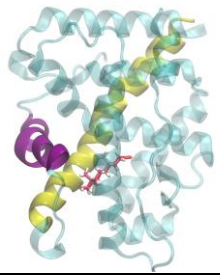
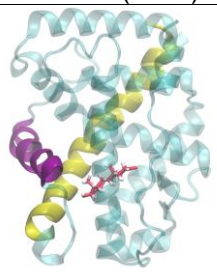
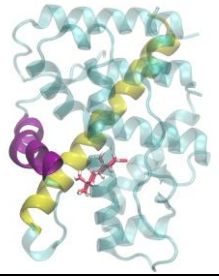
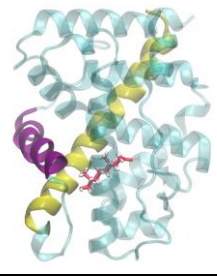
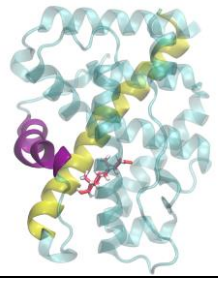
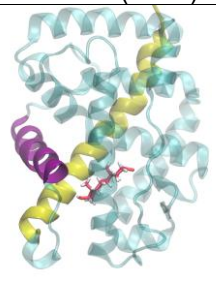
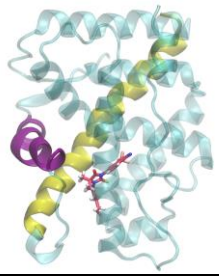
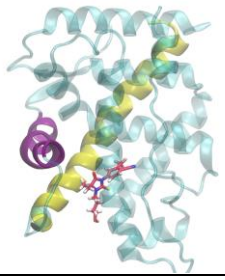
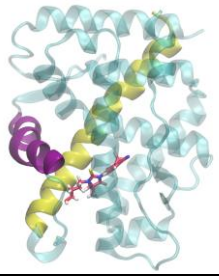
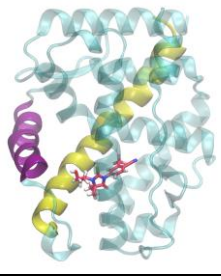
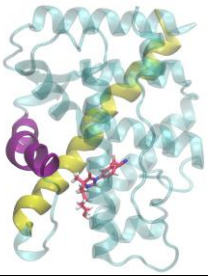
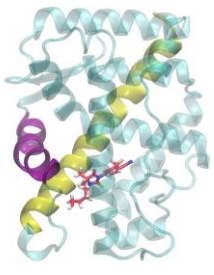
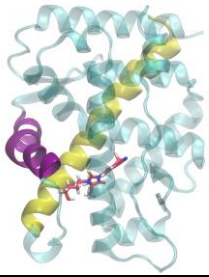
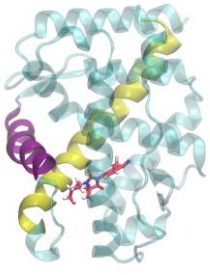
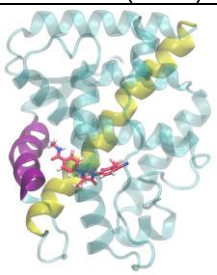
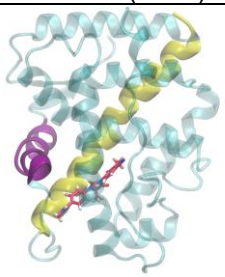
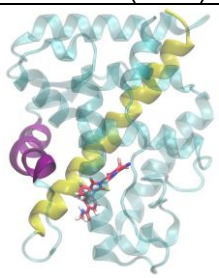
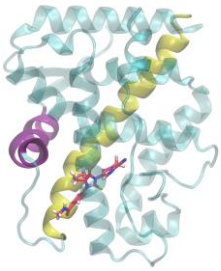
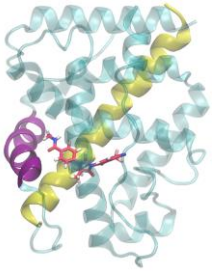
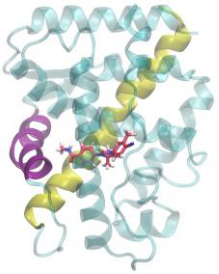
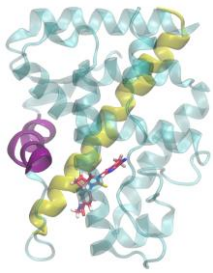
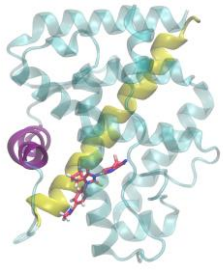
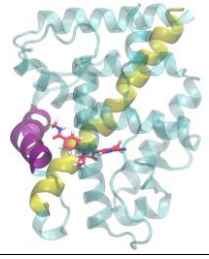
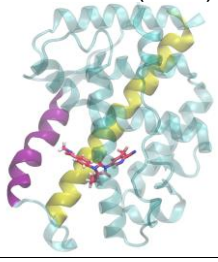
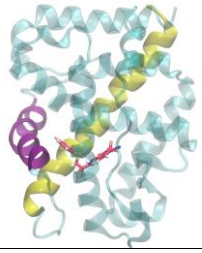
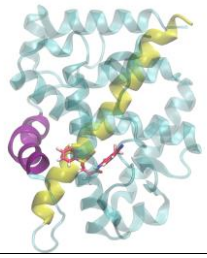



**Figure S13**. Conformational changes of the helix 11 (H11) in AR bound to apalutamide, observed from the MD and the aMD simulations: (A) relative angles and (B) minimal distance between H11 and H12 observed from the MD and the aMD simulations.

| 2AXA+ENZ (Conf. 1) | | 2AXA+ENZ (Conf. 2) | |
|---|---|---|---|
| **MD** | **aMD** | **MD** | **aMD** |
| Cluster 1 (15 %) | Cluster 1 (13 %) | Cluster 1 (25 %) | Cluster 1 (17 %) |
|  |  |  |  |
| Cluster 2 (15 %) | Cluster 2 (13 %) | Cluster 2 (13 %) | Cluster 2 (14 %) |
|  |  |  |  |

| 2PIP+ENZ (Conf. 2) | | 2AXA in *apo* | |
|---|---|---|---|
| **MD** | **aMD** | **MD** | **aMD** |
| Cluster 1 (15 %) | Cluster 1 (14 %) | Cluster 1 (18 %) | Cluster 1 (19 %) |
|  |  |  |  |
| Cluster 2 (13 %) | Cluster 2 (13 %) | Cluster 2 (16 %) | Cluster 2 (13 %) |
|  |  |  |  |
| **2AXA+DHT** | | **2PIP+DHT** | |
| **MD** | **aMD** | **MD** | **aMD** |
| Cluster 1 (15 %) | Cluster 1 (18 %) | Cluster 1 (15 %) | Cluster 1 (18 %) |
|  |  |  |  |
| Cluster 2 (13 %) | Cluster 2 (14 %) | Cluster 2 (13 %) | Cluster 2 (14 %) |
|  |  |  |  |
| **2AXA+RU5 (Conf. 1)** | | **2AXA+RU5 (Conf. 2)** | |
| **MD** | **aMD** | **MD** | **aMD** |
| Cluster 1 (15 %) | Cluster 1 (15 %) | Cluster 1 (17 %) | Cluster 1 (14 %) |

| | | | |
|---|---|---|---|
|  |  |  |  |
| Cluster 2 (12 %) | Cluster 2 (13 %) | Cluster 2 (14 %) | Cluster 2 (14 %) |
|  |  |  |  |
| **2AXA(F876L)+ENZ** | | **2AXA+APL (Conf. 1)** | |
| **MD** | **aMD** | **MD** | **aMD** |
| Cluster 1 (18 %) | Cluster 1 (14 %) | Cluster 1 (16 %) | Cluster 1 (18 %) |
|  |  |  |  |
| Cluster 2 (16 %) | Cluster 2 (13 %) | Cluster 2 (12 %) | Cluster 2 (13 %) |
|  |  |  |  |
| **2AXA+APL (Conf. 2)** | | **2AXA+BCA** | |
| **MD** | **aMD** | **MD** | **aMD** |
| Cluster 1 (16 %) | Cluster 1 (15 %) | Cluster 1 (18 %) | Cluster 1 (15 %) |
|  |  |  |  |
| Cluster 2 (12 %) | Cluster 2 (13 %) | Cluster 2 (12 %) | Cluster 2 (13 %) |

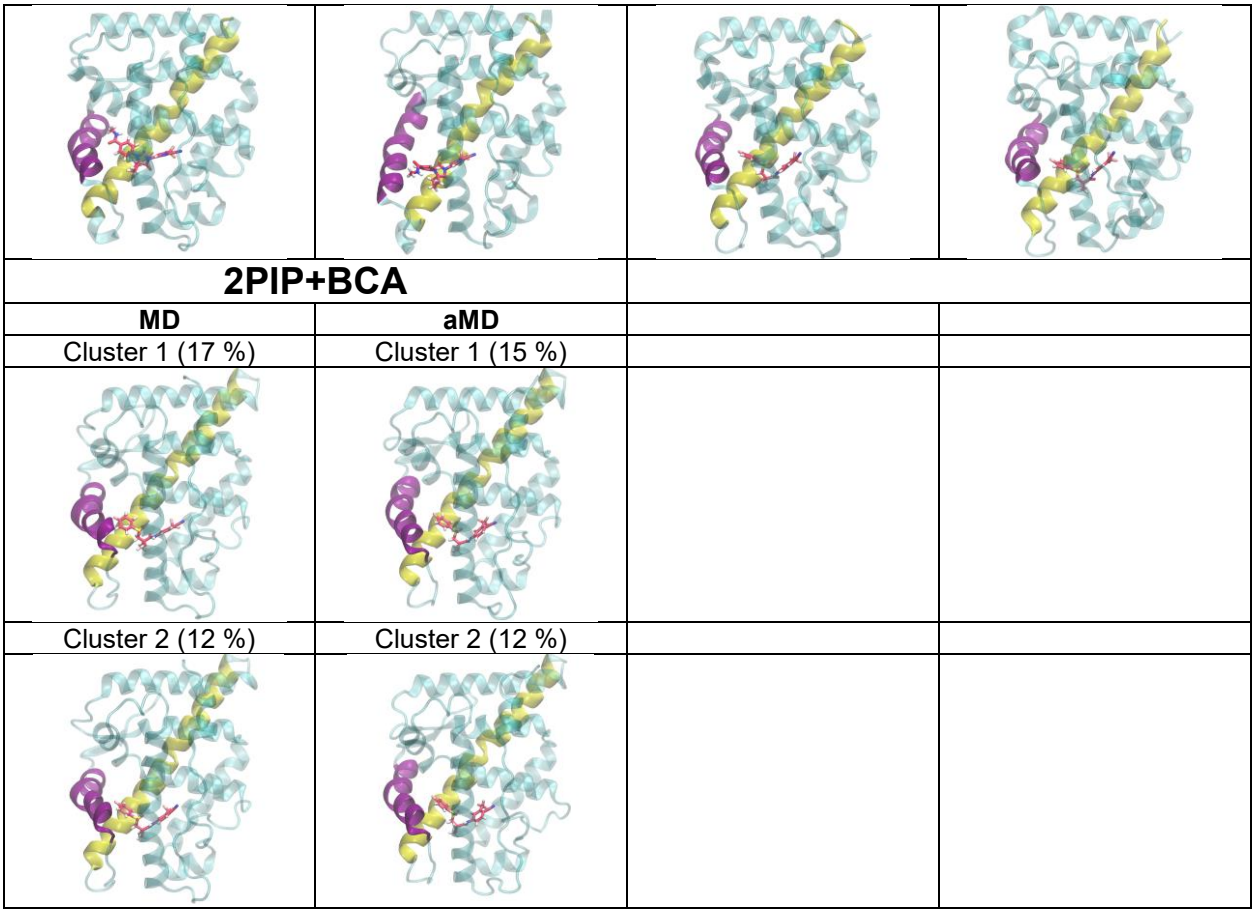



**Figure S14**. Summary of structural clustering analysis of the MD and aMD trajectories. For each 250 ns MD and aMD simulation trajectories, we applied K-means clustering algorithm implemented in MDAnalysis that classified the conformational ensemble into 10 structural clusters. Backbone RMSD was used as the measure of structural similarities. Helix 11 and 12 are highlighted in purple and yellow, respectively. Ligands are color coded in red.

# Supplementary Tables

## Optimized Coordinates, RESP Charges, and Energies of the Ligands of AR

Bicalutamide

| | Configuration 1 | | | | Configuration 2 | | | Partial |
|---|---|---|---|---|---|---|---|---|
| Atom | X | Y | Z | Atom | X | Y | Z | Charge |
| C | 52.703 | 48.479 | 42.262 | C | 8.791 | 1.658 | 7.152 | -0.087060 |
| C | 53.571 | 49.427 | 41.735 | C | 9.361 | 0.444 | 7.511 | -0.316968 |
| C | 53.027 | 50.574 | 41.171 | C | 8.966 | -0.697 | 6.826 | 0.442890 |
| F | 53.865 | 51.495 | 40.660 | F | 9.517 | -1.874 | 7.172 | -0.220835 |
| C | 51.662 | 50.815 | 41.106 | C | 8.027 | -0.683 | 5.803 | -0.316968 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **C** | 50.799 | 49.862 | 41.636 | **C** | 7.460 | 0.534 | 5.446 | -0.087060 |
| **C** | 51.329 | 48.707 | 42.208 | **C** | 7.848 | 1.688 | 6.124 | -0.026580 |
| **C** | 50.141 | 47.997 | 44.651 | **C** | 8.337 | 3.914 | 4.452 | -0.489743 |
| **C** | 49.484 | 46.956 | 45.595 | **C** | 7.989 | 5.341 | 3.989 | 0.477428 |
| **O** | 50.327 | 45.850 | 45.760 | **O** | 7.840 | 6.242 | 5.071 | -0.657679 |
| **C** | 49.317 | 47.586 | 46.980 | **C** | 9.127 | 5.866 | 3.110 | -0.481787 |
| **C** | 48.136 | 46.452 | 45.013 | **C** | 6.711 | 5.288 | 3.112 | 0.707155 |
| **O** | 48.056 | 45.315 | 44.579 | **O** | 6.657 | 4.545 | 2.143 | -0.595838 |
| **N** | 47.111 | 47.354 | 45.010 | **N** | 5.739 | 6.154 | 3.506 | -0.620068 |
| **C** | 45.850 | 47.227 | 44.414 | **C** | 4.468 | 6.341 | 2.961 | 0.386999 |
| **C** | 45.482 | 46.114 | 43.648 | **C** | 4.014 | 5.631 | 1.841 | -0.213291 |
| **C** | 44.943 | 48.276 | 44.592 | **C** | 3.627 | 7.275 | 3.575 | -0.323835 |
| **C** | 43.687 | 48.220 | 44.013 | **C** | 2.355 | 7.503 | 3.080 | -0.092118 |
| **C** | 43.309 | 47.114 | 43.246 | **C** | 1.894 | 6.801 | 1.961 | -0.044519 |
| **C** | 44.223 | 46.062 | 43.071 | **C** | 2.739 | 5.862 | 1.349 | -0.060682 |
| **C** | 43.841 | 44.855 | 42.245 | **C** | 2.269 | 5.090 | 0.138 | 0.613358 |
| **F** | 42.746 | 44.245 | 42.741 | **F** | 1.158 | 4.375 | 0.407 | -0.200591 |
| **F** | 43.558 | 45.197 | 40.973 | **F** | 1.966 | 5.915 | -0.885 | -0.200591 |
| **F** | 44.818 | 43.938 | 42.200 | **F** | 3.193 | 4.228 | -0.311 | -0.200591 |
| **H** | 53.091 | 47.564 | 42.698 | **H** | 9.066 | 2.569 | 7.672 | 0.185333 |
| **H** | 54.644 | 49.284 | 41.751 | **H** | 10.094 | 0.374 | 8.306 | 0.203999 |
| **H** | 51.291 | 51.722 | 40.645 | **H** | 7.749 | -1.605 | 5.306 | 0.203999 |
| **H** | 49.726 | 50.008 | 41.590 | **H** | 6.715 | 0.584 | 4.660 | 0.185333 |
| **H** | 49.617 | 48.956 | 44.651 | **H** | 8.359 | 3.233 | 3.598 | 0.181527 |
| **H** | 51.170 | 48.149 | 44.985 | **H** | 9.304 | 3.907 | 4.960 | 0.181527 |
| **H** | 50.165 | 45.235 | 45.030 | **H** | 7.582 | 5.762 | 5.877 | 0.399013 |
| **H** | 50.309 | 47.779 | 47.396 | **H** | 10.057 | 5.874 | 3.682 | 0.143094 |
| **H** | 48.774 | 48.534 | 46.958 | **H** | 9.247 | 5.247 | 2.219 | 0.143094 |
| **H** | 48.796 | 46.890 | 47.641 | **H** | 8.900 | 6.890 | 2.801 | 0.143094 |
| **H** | 46.181 | 45.304 | 43.508 | **H** | 4.662 | 4.907 | 1.370 | 0.213813 |
| **H** | 45.218 | 49.142 | 45.185 | **H** | 3.969 | 7.824 | 4.447 | 0.198380 |
| **H** | 42.988 | 49.036 | 44.155 | **H** | 1.708 | 8.227 | 3.560 | 0.176029 |
| **S** | 50.224 | 47.501 | 42.912 | **S** | 7.148 | 3.243 | 5.636 | 0.878336 |
| **O** | 50.864 | 46.186 | 42.832 | **O** | 7.180 | 4.154 | 6.797 | -0.534570 |
| **O** | 48.894 | 47.697 | 42.329 | **O** | 5.873 | 3.002 | 4.963 | -0.534570 |
| **C** | 41.996 | 47.102 | 42.666 | **C** | 0.568 | 7.073 | 1.482 | 0.351347 |
| **N** | 40.929 | 47.129 | 42.213 | **N** | -0.507 | 7.320 | 1.124 | -0.449811 |
| **H** | 47.289 | 48.250 | 45.440 | **H** | 5.988 | 6.704 | 4.320 | 0.340009 |

Enzalutamide

| | **Conformation 1** | | | | **Conformation 2** | | | **Partial** |
|---|---|---|---|---|---|---|---|---|
| **Atom** | X | Y | Z | **Atom** | X | Y | Z | **Charge** |
| **C** | 4.205 | 5.459 | 3.414 | **C** | 4.236 | 5.409 | 3.423 | 0.051961 |
| **C** | 3.732 | 4.887 | 2.235 | **C** | 3.614 | 5.258 | 2.188 | -0.179428 |
| **C** | 3.496 | 6.460 | 4.062 | **C** | 3.716 | 6.256 | 4.392 | -0.174677 |
| **C** | 2.295 | 6.904 | 3.523 | **C** | 2.544 | 6.953 | 4.128 | -0.109482 |
| **C** | 1.814 | 6.350 | 2.336 | **C** | 1.906 | 6.810 | 2.893 | 0.008209 |
| **C** | 2.540 | 5.334 | 1.689 | **C** | 2.449 | 5.959 | 1.916 | -0.032321 |
| **C** | 2.027 | 4.723 | 0.405 | **C** | 1.772 | 5.793 | 0.575 | 0.607718 |
| **F** | 0.817 | 4.156 | 0.576 | **F** | 0.527 | 5.299 | 0.708 | -0.196866 |
| **F** | 1.897 | 5.647 | -0.565 | **F** | 1.663 | 6.968 | -0.073 | -0.196866 |
| **F** | 2.849 | 3.770 | -0.061 | **F** | 2.447 | 4.957 | -0.229 | -0.196866 |
| **H** | 4.301 | 4.103 | 1.751 | **H** | 4.041 | 4.593 | 1.448 | 0.181595 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **H** | 3.879 | 6.893 | 4.978 | **H** | 4.216 | 6.363 | 5.347 | 0.178307 |
| **H** | 1.730 | 7.686 | 4.016 | **H** | 2.121 | 7.614 | 4.875 | 0.175781 |
| **C** | 0.571 | 6.848 | 1.810 | **C** | 0.696 | 7.553 | 2.665 | 0.324590 |
| **N** | -0.432 | 7.273 | 1.415 | **N** | -0.277 | 8.165 | 2.516 | -0.422226 |
| **C** | 6.951 | 4.004 | 5.455 | **C** | 7.666 | 3.977 | 3.528 | 0.317912 |
| **N** | 5.423 | 4.992 | 3.982 | **N** | 5.443 | 4.695 | 3.669 | 0.183156 |
| **C** | 5.481 | 4.287 | 5.175 | **C** | 6.636 | 4.980 | 3.023 | 0.380350 |
| **O** | 4.533 | 3.965 | 5.855 | **O** | 6.810 | 5.861 | 2.213 | -0.501238 |
| **C** | 6.696 | 5.217 | 3.443 | **C** | 5.562 | 3.602 | 4.537 | -0.288105 |
| **S** | 7.010 | 6.053 | 2.048 | **S** | 4.334 | 2.963 | 5.448 | -0.260448 |
| **N** | 7.579 | 4.636 | 4.280 | **N** | 6.844 | 3.191 | 4.467 | 0.300095 |
| **C** | 7.375 | 4.687 | 6.758 | **C** | 8.170 | 3.120 | 2.364 | -0.463683 |
| **C** | 7.199 | 2.494 | 5.496 | **C** | 8.808 | 4.705 | 4.239 | -0.463683 |
| **H** | 8.438 | 4.513 | 6.940 | **H** | 8.885 | 2.378 | 2.729 | 0.136468 |
| **H** | 7.195 | 5.765 | 6.715 | **H** | 7.345 | 2.603 | 1.868 | 0.136468 |
| **H** | 6.804 | 4.266 | 7.588 | **H** | 8.673 | 3.761 | 1.638 | 0.136468 |
| **H** | 8.258 | 2.296 | 5.682 | **H** | 9.540 | 3.982 | 4.609 | 0.136468 |
| **H** | 6.614 | 2.057 | 6.308 | **H** | 9.305 | 5.372 | 3.530 | 0.136468 |
| **H** | 6.908 | 2.021 | 4.555 | **H** | 8.436 | 5.297 | 5.079 | 0.136468 |
| **C** | 8.992 | 4.694 | 4.103 | **C** | 7.357 | 2.073 | 5.188 | -0.007598 |
| **C** | 9.690 | 5.803 | 4.568 | **C** | 7.259 | 0.803 | 4.632 | -0.287575 |
| **C** | 9.664 | 3.637 | 3.496 | **C** | 7.974 | 2.262 | 6.422 | -0.254297 |
| **C** | 11.064 | 5.829 | 4.412 | **C** | 7.788 | -0.265 | 5.335 | 0.361535 |
| **H** | 9.182 | 6.640 | 5.033 | **H** | 6.773 | 0.638 | 3.678 | 0.190575 |
| **C** | 11.045 | 3.697 | 3.363 | **C** | 8.498 | 1.167 | 7.094 | 0.033293 |
| **H** | 9.110 | 2.784 | 3.124 | **H** | 8.035 | 3.255 | 6.852 | 0.166275 |
| **C** | 11.785 | 4.793 | 3.817 | **C** | 8.420 | -0.128 | 6.571 | -0.298023 |
| **H** | 11.591 | 2.886 | 2.896 | **H** | 8.985 | 1.290 | 8.054 | 0.143412 |
| **F** | 11.704 | 6.930 | 4.879 | **F** | 7.669 | -1.486 | 4.758 | -0.222517 |
| **C** | 13.282 | 4.730 | 3.612 | **C** | 9.035 | -1.232 | 7.403 | 0.728769 |
| **O** | 13.791 | 3.714 | 3.138 | **O** | 9.655 | -0.950 | 8.428 | -0.586797 |
| **N** | 14.020 | 5.802 | 3.955 | **N** | 8.876 | -2.504 | 6.993 | -0.488388 |
| **H** | 13.571 | 6.621 | 4.332 | **H** | 8.356 | -2.700 | 6.153 | 0.351799 |
| **C** | 15.459 | 5.807 | 3.764 | **C** | 9.432 | -3.606 | 7.757 | -0.285454 |
| **H** | 15.921 | 4.973 | 4.298 | **H** | 10.509 | -3.478 | 7.886 | 0.137466 |
| **H** | 15.710 | 5.717 | 2.704 | **H** | 8.971 | -3.667 | 8.747 | 0.137466 |
| **H** | 15.856 | 6.746 | 4.150 | **H** | 9.242 | -4.533 | 7.215 | 0.137466 |

Apalutamide

| **Conformer 1** | | | | **Conformer 2** | | | | **Partial** |
|---|---|---|---|---|---|---|---|---|
| **Atom** | X | Y | Z | **Atom** | X | Y | Z | **Charge** |
| **C** | -2.390 | 0.560 | -0.385 | **C** | 3.877 | 5.702 | 2.718 | -0.256829 |
| **C** | -3.058 | -0.376 | 0.392 | **C** | 2.631 | 5.099 | 2.631 | 0.099050 |
| **C** | -3.069 | 1.218 | -1.407 | **C** | 3.987 | 7.079 | 2.541 | 0.358040 |
| **N** | -4.354 | 0.986 | -1.676 | **N** | 2.936 | 7.855 | 2.290 | -0.585608 |
| **C** | -4.994 | 0.078 | -0.938 | **C** | 1.735 | 7.277 | 2.215 | 0.569683 |
| **C** | -4.392 | -0.628 | 0.111 | **C** | 1.527 | 5.902 | 2.380 | -0.362097 |
| **C** | -5.170 | -1.638 | 0.926 | **C** | 0.147 | 5.294 | 2.273 | 0.672007 |
| **F** | -6.235 | -1.072 | 1.524 | **F** | -0.686 | 5.795 | 3.201 | -0.204484 |
| **F** | -5.629 | -2.642 | 0.158 | **F** | -0.404 | 5.534 | 1.070 | -0.204484 |
| **F** | -4.414 | -2.179 | 1.892 | **F** | 0.181 | 3.963 | 2.440 | -0.204484 |
| **H** | -2.550 | -0.888 | 1.199 | **H** | 2.524 | 4.029 | 2.758 | 0.159698 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **H** | -2.562 | 1.952 | -2.024 | **H** | 4.954 | 7.567 | 2.603 | 0.108896 |
| **C** | -6.380 | -0.130 | -1.297 | **C** | 0.638 | 8.183 | 1.946 | 0.208906 |
| **N** | -7.491 | -0.285 | -1.591 | **N** | -0.232 | 8.915 | 1.731 | -0.376482 |
| **C** | 0.892 | 2.055 | 0.429 | **C** | 7.115 | 3.920 | 2.626 | 0.241445 |
| **N** | -1.033 | 0.876 | -0.140 | **N** | 5.044 | 4.932 | 2.944 | 0.066725 |
| **C** | -0.610 | 2.134 | 0.280 | **C** | 6.082 | 4.842 | 2.021 | 0.480404 |
| **O** | -1.335 | 3.083 | 0.485 | **O** | 6.118 | 5.402 | 0.949 | -0.497923 |
| **C** | 0.046 | -0.010 | -0.294 | **C** | 5.299 | 4.169 | 4.093 | -0.033217 |
| **S** | -0.075 | -1.582 | -0.799 | **S** | 4.299 | 4.052 | 5.408 | -0.288007 |
| **N** | 1.158 | 0.678 | 0.039 | **N** | 6.498 | 3.582 | 3.903 | -0.059705 |
| **C** | 1.639 | 3.225 | -0.269 | **C** | 7.580 | 2.797 | 1.662 | -0.222753 |
| **C** | 1.405 | 2.593 | 1.795 | **C** | 8.555 | 4.498 | 2.584 | -0.222753 |
| **C** | 2.472 | 0.123 | 0.014 | **C** | 7.114 | 2.707 | 4.848 | 0.120609 |
| **C** | 3.244 | 0.238 | -1.140 | **C** | 6.866 | 1.340 | 4.775 | -0.187461 |
| **C** | 2.969 | -0.513 | 1.149 | **C** | 7.970 | 3.227 | 5.816 | -0.187461 |
| **C** | 4.538 | -0.265 | -1.147 | **C** | 7.494 | 0.481 | 5.671 | -0.057629 |
| **H** | 2.823 | 0.701 | -2.027 | **H** | 6.173 | 0.958 | 4.033 | 0.151698 |
| **C** | 4.260 | -1.021 | 1.130 | **C** | 8.589 | 2.365 | 6.712 | -0.057629 |
| **H** | 2.345 | -0.609 | 2.029 | **H** | 8.135 | 4.298 | 5.871 | 0.151698 |
| **C** | 5.059 | -0.890 | -0.009 | **C** | 8.367 | 0.988 | 6.637 | -0.210990 |
| **H** | 4.663 | -1.531 | 2.003 | **H** | 9.249 | 2.750 | 7.481 | 0.135122 |
| **H** | 5.128 | -0.196 | -2.058 | **H** | 7.268 | -0.580 | 5.625 | 0.135122 |
| **C** | 6.448 | -1.462 | 0.034 | **C** | 9.068 | 0.114 | 7.642 | 0.769186 |
| **O** | 6.714 | -2.450 | 0.719 | **O** | 9.396 | 0.551 | 8.745 | -0.572962 |
| **N** | 7.385 | -0.826 | -0.718 | **N** | 9.314 | -1.162 | 7.271 | -0.568693 |
| **H** | 7.161 | 0.062 | -1.140 | **H** | 9.170 | -1.434 | 6.311 | 0.322294 |
| **C** | 8.762 | -1.282 | -0.746 | **C** | 9.991 | -2.089 | 8.158 | -0.137092 |
| **H** | 9.227 | -1.205 | 0.247 | **H** | 11.031 | -1.792 | 8.328 | 0.102635 |
| **H** | 8.808 | -2.328 | -1.073 | **H** | 9.481 | -2.125 | 9.122 | 0.102635 |
| **H** | 9.318 | -0.660 | -1.458 | **H** | 9.971 | -3.081 | 7.705 | 0.102635 |
| **C** | 1.725 | 3.938 | 1.100 | **C** | 8.812 | 3.662 | 1.309 | 0.011207 |
| **H** | 2.311 | 2.058 | 2.088 | **H** | 9.132 | 4.130 | 3.436 | 0.085995 |
| **H** | 0.691 | 2.586 | 2.616 | **H** | 8.642 | 5.584 | 2.522 | 0.085995 |
| **H** | 2.682 | 4.397 | 1.350 | **H** | 9.770 | 3.145 | 1.251 | 0.042535 |
| **H** | 0.924 | 4.664 | 1.231 | **H** | 8.654 | 4.244 | 0.400 | 0.042535 |
| **H** | 1.111 | 3.720 | -1.084 | **H** | 6.886 | 2.526 | 0.863 | 0.085995 |
| **H** | 2.624 | 2.890 | -0.612 | **H** | 7.856 | 1.905 | 2.228 | 0.085995 |

RU59063

| Atom | X | Y | Z | Partial Charge |
|---|---|---|---|---|
| **C** | -2.188 | 1.875 | -0.754 | -0.159377 |
| **N** | -6.629 | 0.050 | -0.629 | -0.423424 |
| **O** | -0.085 | 3.084 | 1.211 | -0.518951 |
| **S** | 0.844 | -0.894 | -1.681 | -0.298643 |
| **C** | -3.551 | 1.618 | -0.836 | -0.100753 |
| **N** | 0.048 | 1.184 | -0.111 | 0.151689 |
| **C** | -4.068 | 0.399 | -0.393 | -0.002819 |
| **N** | 2.241 | 0.976 | -0.326 | 0.237912 |
| **C** | -3.203 | -0.567 | 0.150 | -0.009725 |
| **C** | -1.845 | -0.303 | 0.240 | -0.164194 |
| **C** | -1.343 | 0.911 | -0.221 | -0.003820 |
| **C** | -3.741 | -1.889 | 0.646 | 0.589287 |

| | | | | |
|---|---|---|---|---|
| **C** | -5.484 | 0.181 | -0.512 | 0.329816 |
| **C** | 2.074 | 2.180 | 0.492 | 0.199879 |
| **C** | 0.556 | 2.253 | 0.611 | 0.485847 |
| **C** | 1.074 | 0.418 | -0.699 | -0.188296 |
| **C** | 2.702 | 2.031 | 1.88 | -0.437683 |
| **C** | 2.579 | 3.436 | -0.228 | -0.437683 |
| **F** | -2.766 | -2.669 | 1.144 | -0.195690 |
| **F** | -4.649 | -1.715 | 1.624 | -0.195690 |
| **F** | -4.340 | -2.578 | -0.339 | -0.195690 |
| **H** | -1.786 | 2.820 | -1.099 | 0.174794 |
| **H** | -4.224 | 2.361 | -1.248 | 0.173601 |
| **H** | -1.173 | -1.043 | 0.654 | 0.174336 |
| **H** | 2.444 | 2.901 | 2.489 | 0.136732 |
| **H** | 2.337 | 1.130 | 2.380 | 0.136732 |
| **H** | 3.791 | 1.972 | 1.797 | 0.136732 |
| **H** | 2.292 | 4.319 | 0.347 | 0.136732 |
| **H** | 3.669 | 3.420 | -0.316 | 0.136732 |
| **H** | 2.147 | 3.511 | -1.230 | 0.136732 |
| **C** | 3.539 | 0.446 | -0.715 | -0.394540 |
| **H** | 3.478 | 0.147 | -1.766 | 0.132834 |
| **H** | 4.265 | 1.261 | -0.642 | 0.132834 |
| **C** | 3.985 | -0.742 | 0.139 | 0.029978 |
| **H** | 4.057 | -0.431 | 1.189 | 0.004581 |
| **H** | 3.214 | -1.518 | 0.080 | 0.004581 |
| **C** | 5.326 | -1.296 | -0.337 | 0.082329 |
| **H** | 6.104 | -0.525 | -0.275 | 0.035469 |
| **H** | 5.255 | -1.596 | -1.389 | 0.035469 |
| **C** | 5.771 | -2.498 | 0.478 | 0.204708 |
| **H** | 5.849 | -2.220 | 1.541 | 0.002094 |
| **H** | 5.021 | -3.298 | 0.394 | 0.002094 |
| **O** | 7.026 | -2.924 | -0.022 | -0.718761 |
| **H** | 7.305 | -3.713 | 0.450 | 0.441214 |

Dihydrotestosterone

| Atom | X | Y | Z | Partial Charge |
|---|---|---|---|---|
| **C** | 2.522 | -1.523 | -0.436 | 0.052432 |
| **C** | 4.026 | -1.486 | -0.128 | -0.249394 |
| **C** | 4.640 | -0.121 | -0.360 | 0.661308 |
| **O** | 5.706 | 0.023 | -0.925 | -0.571579 |
| **C** | 3.844 | 1.052 | 0.170 | -0.448545 |
| **C** | 2.349 | 0.951 | -0.170 | 0.301034 |
| **C** | 1.572 | 2.157 | 0.359 | -0.210028 |
| **C** | 0.122 | 2.125 | -0.118 | -0.101511 |
| **C** | -0.574 | 0.808 | 0.233 | 0.038721 |
| **C** | 0.243 | -0.412 | -0.266 | -0.016783 |
| **C** | 1.714 | -0.403 | 0.256 | 0.061847 |
| **C** | -0.497 | -1.741 | -0.018 | 0.001121 |
| **C** | -1.943 | -1.742 | -0.543 | -0.372913 |
| **C** | -2.734 | -0.552 | 0.003 | 0.039673 |

| | | | | |
|---|---|---|---|---|
| **C** | -1.976 | 0.736 | -0.364 | 0.074313 |
| **C** | -2.983 | 1.860 | -0.075 | -0.317119 |
| **C** | -4.360 | 1.219 | -0.389 | -0.043855 |
| **C** | -4.075 | -0.262 | -0.706 | 0.488893 |
| **O** | -5.178 | -1.053 | -0.303 | -0.769669 |
| **C** | -2.975 | -0.709 | 1.512 | -0.281744 |
| **C** | 1.759 | -0.610 | 1.781 | -0.441036 |
| **H** | 2.139 | -2.506 | -0.144 | 0.002633 |
| **H** | 2.378 | -1.440 | -1.522 | 0.002633 |
| **H** | 4.193 | -1.735 | 0.929 | 0.075237 |
| **H** | 4.576 | -2.218 | -0.724 | 0.075237 |
| **H** | 3.981 | 1.086 | 1.260 | 0.114584 |
| **H** | 4.276 | 1.971 | -0.236 | 0.114584 |
| **H** | 2.274 | 0.985 | -1.269 | -0.012647 |
| **H** | 1.609 | 2.171 | 1.457 | 0.061152 |
| **H** | 2.058 | 3.080 | 0.021 | 0.061152 |
| **H** | -0.435 | 2.966 | 0.311 | 0.035775 |
| **H** | 0.100 | 2.258 | -1.210 | 0.035775 |
| **H** | -0.666 | 0.760 | 1.328 | 0.048034 |
| **H** | 0.316 | -0.293 | -1.361 | 0.004315 |
| **H** | -0.505 | -1.968 | 1.054 | 0.043298 |
| **H** | 0.044 | -2.562 | -0.500 | 0.043298 |
| **H** | -2.424 | -2.694 | -0.280 | 0.098011 |
| **H** | -1.925 | -1.684 | -1.641 | 0.098011 |
| **H** | -1.840 | 0.709 | -1.460 | 0.008858 |
| **H** | -2.922 | 2.172 | 0.974 | 0.090598 |
| **H** | -2.790 | 2.750 | -0.681 | 0.090598 |
| **H** | -5.038 | 1.264 | 0.468 | 0.033708 |
| **H** | -4.869 | 1.708 | -1.224 | 0.033708 |
| **H** | -3.918 | -0.385 | -1.790 | -0.035722 |
| **H** | -5.055 | -1.949 | -0.630 | 0.431203 |
| **H** | -3.582 | -1.600 | 1.700 | 0.076758 |
| **H** | -2.040 | -0.814 | 2.067 | 0.076758 |
| **H** | -3.516 | 0.141 | 1.935 | 0.076758 |
| **H** | 1.458 | -1.629 | 2.040 | 0.106842 |
| **H** | 1.097 | 0.076 | 2.315 | 0.106842 |
| **H** | 2.764 | -0.463 | 2.187 | 0.106842 |

DFT Computed Energies of the Ligands

| LIGAND | CONF. | E(SCF)* | ZPE | -TS(GAS) | ΔG | ΔΔG |
|---|---|---|---|---|---|---|
| **BICALUTAMIDE** | 1 | -51752.502 | 192.12 | -55.00 | -1193286.39 | 5.61 |
| | 2 | -51752.770 | 192.53 | -54.54 | -1193292.00 | 0.00 |
| **ENZALUTAMIDE** | 1 | -53783.860 | 219.18 | -58.78 | -1240105.66 | 1.47 |
| | 2 | -53783.860 | 218.97 | -58.78 | -1240107.13 | 0.00 |
| **APALUTAMIDE** | 1 | -52555.982 | 221.11 | -65.92 | -1211788.24 | 1.86 |
| | 2 | -52555.980 | 221.02 | -60.19 | -1211790.10 | 0.00 |
| **RU59063** | | -45463.81 | 213.22 | -53.50 | -1048243.63 | |
| **DHT** | | -24283.24 | 293.79 | -41.12 | -559719.37 | |

For bicalutamide, enzalutamide and apalutamide, geometries were optimized at the ωB97X-D/6-31+G(d,p)/IEFPCM(diethylether) level of the theory. For RU59063 and dihydrotestosterone (DHT), the geometries were obtained using the ωB97X-D/6-31+G(d,p) level of the theory. Vibrational frequencies of the optimized geometries were computed to obtain thermal corrections to the Gibbs free energies including zero-point energy (ZPE) and entropic contribution (-TS). The Gibbs free energy of molecule (ΔG) is the sum of E(SCF), ZPE, -TS, and the thermal corrections. Energy unit is kcal/mol, except for the SCF energy (E(SCF) that is in eV. Entropic contribution in gas (-TS(gas)) phase is measured at 298.15 K.