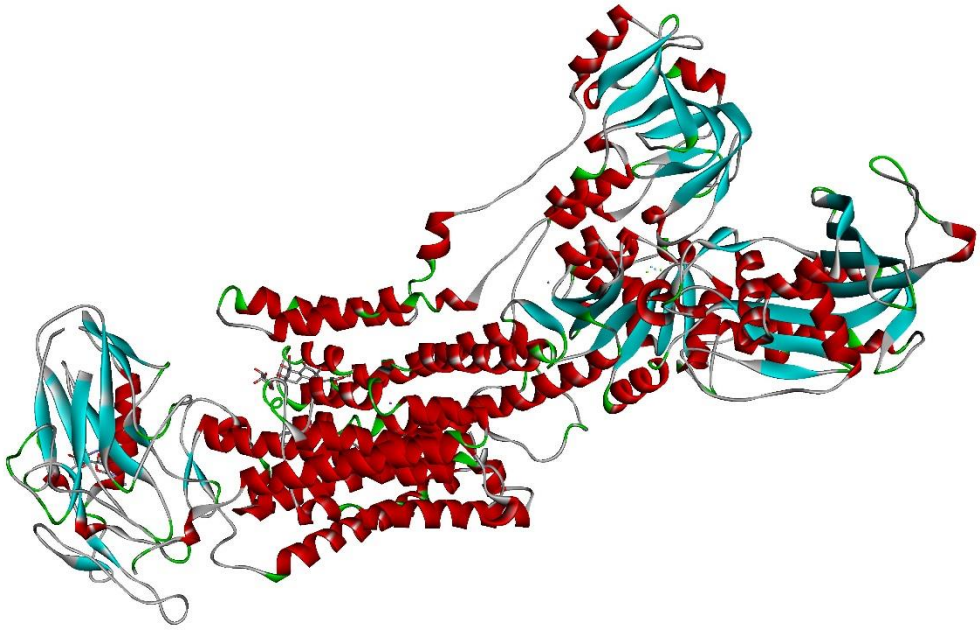

Figure S1 Crystal structure of the sodium-potassium pump (Na^+-K^+-ATPase) with bound potassium and ouabain (PDB ID: 3A3Y)

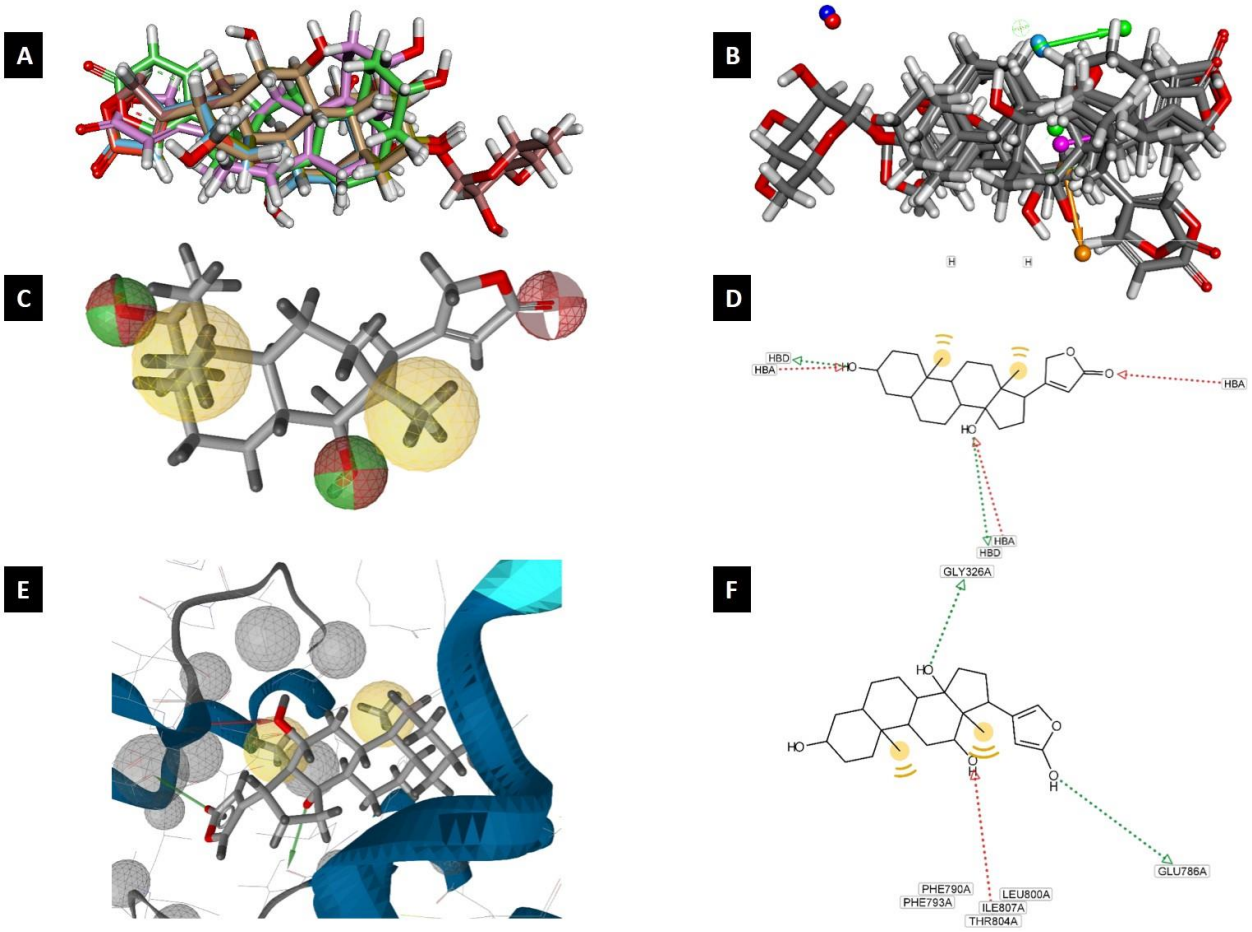

Figure S2 Pharmacophore model: (A) Aligned molecules, (B) Shared pharmacophore features, (C) PhytochemicalScout pharmacophore model generated from Digoxigenin format (hydrogen bond Donor: green sphere, hydrogen bonds Acceptor: Red sphere and ionizable area: Blue asterisk and Aromatic rings), (D) 2D representation of mapped pharmacophore feature, (E) Structure-based mapped pharmacophore feature in 3D format, and (F) 2D representation of pharmacophore feature with amino acid residues

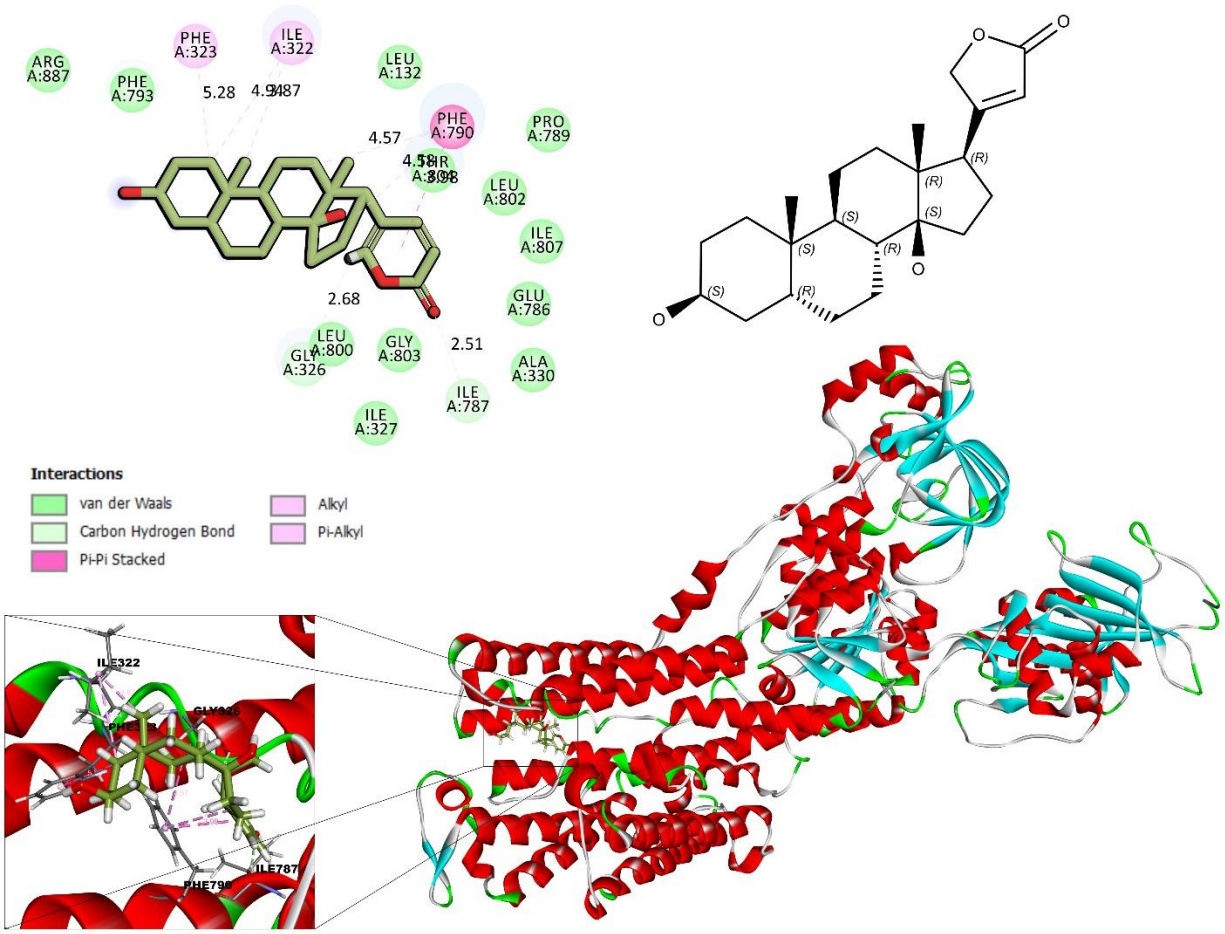

Figure S3 Docked pose of 3A3Y protein with ligand Digitoxigenin (Blue color) docked pose and Protein– ligand interaction maps developed from Accelrys Discovery studio visualizer 2016 (van der Waals-Light Green, conventional hydrogen bonds-Green color, carbon-hydrogen-White color, unfavorable donor-donor-Red color, π- sigma-Purple color, π- π-T shaped-Dark pink color, alkyl and π- alkyl-Light Pink color)

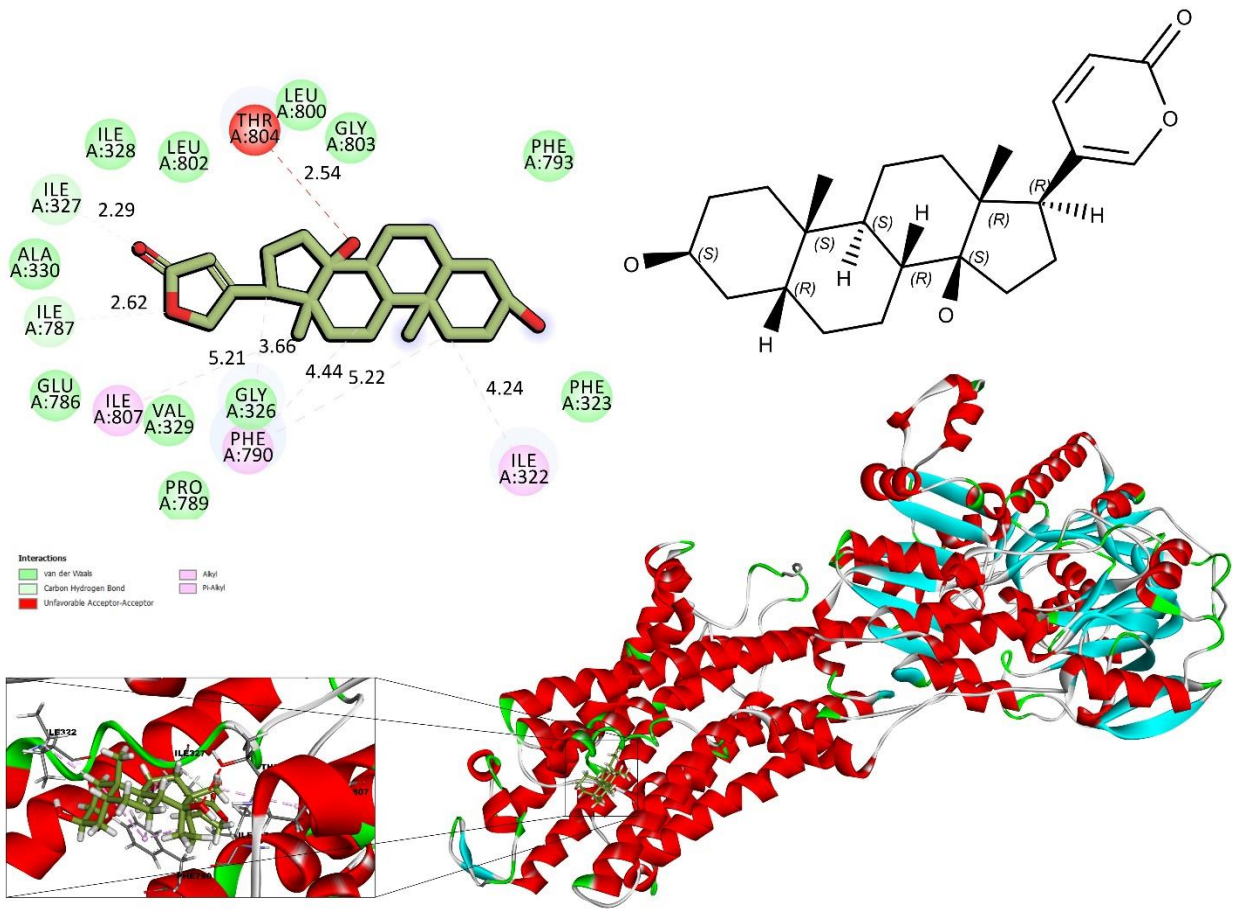

Figure S4 Docked pose of 3A3Y protein with ligand Bufalin (Blue color) docked pose and Protein– ligand interaction maps developed from Accelrys Discovery studio visualizer 2016 (van der Waals-Light Green, conventional hydrogen bonds-Green color, carbon-hydrogen-White color, unfavorable donor-donor-Red color, π- sigma-Purple color, π- π-T shaped-Dark pink color, alkyl and π- alkyl-Light Pink color)

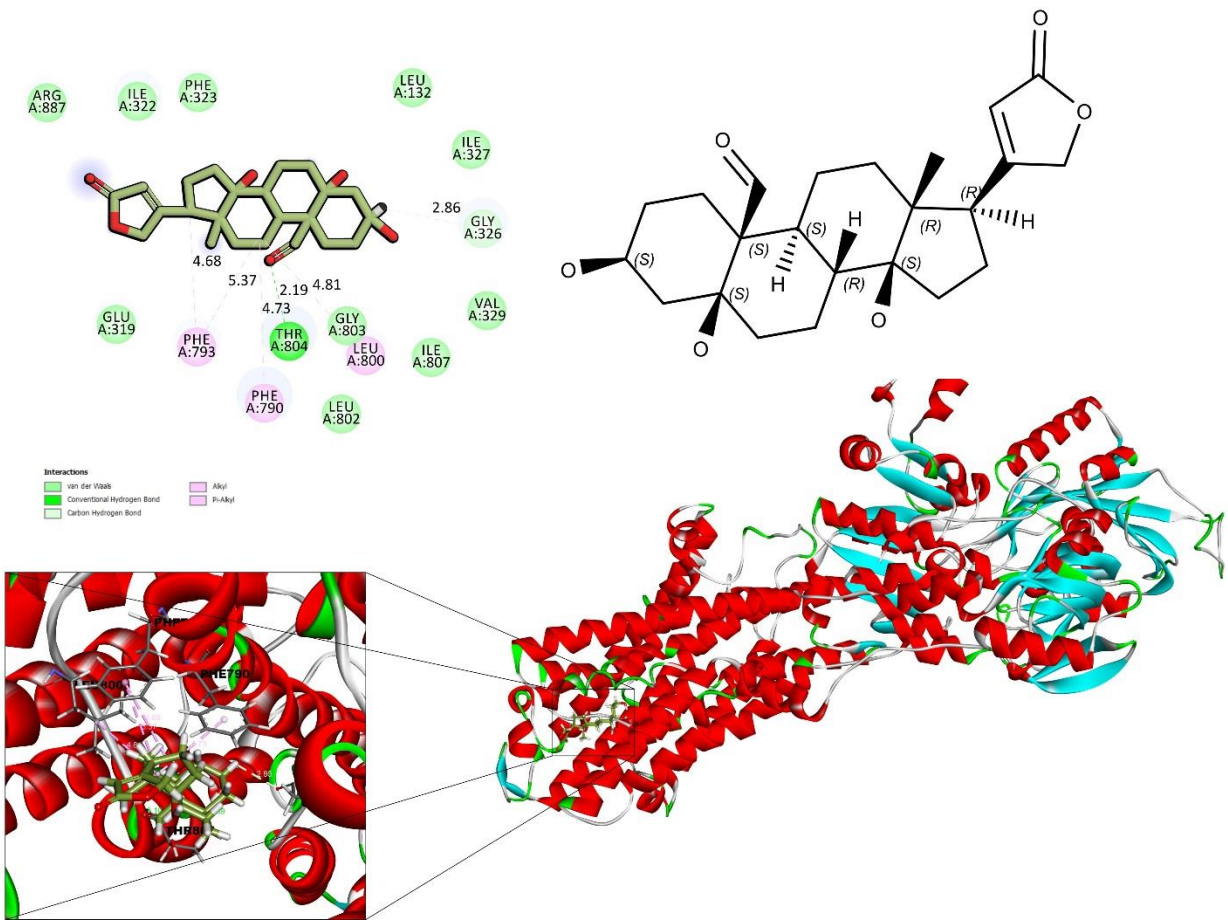

Figure S5 Docked pose of 3A3Y protein with ligand Strophanthidin (Blue color) docked pose and Protein– ligand interaction maps developed from Accelrys Discovery studio visualizer 2016 (van der Waals-Light Green, conventional hydrogen bonds-Green color, carbon-hydrogen-White color, unfavorable donor-donor-Red color, π- sigma-Purple color, π- π-T shaped-Dark pink color, alkyl and π- alkyl-Light Pink color ligand

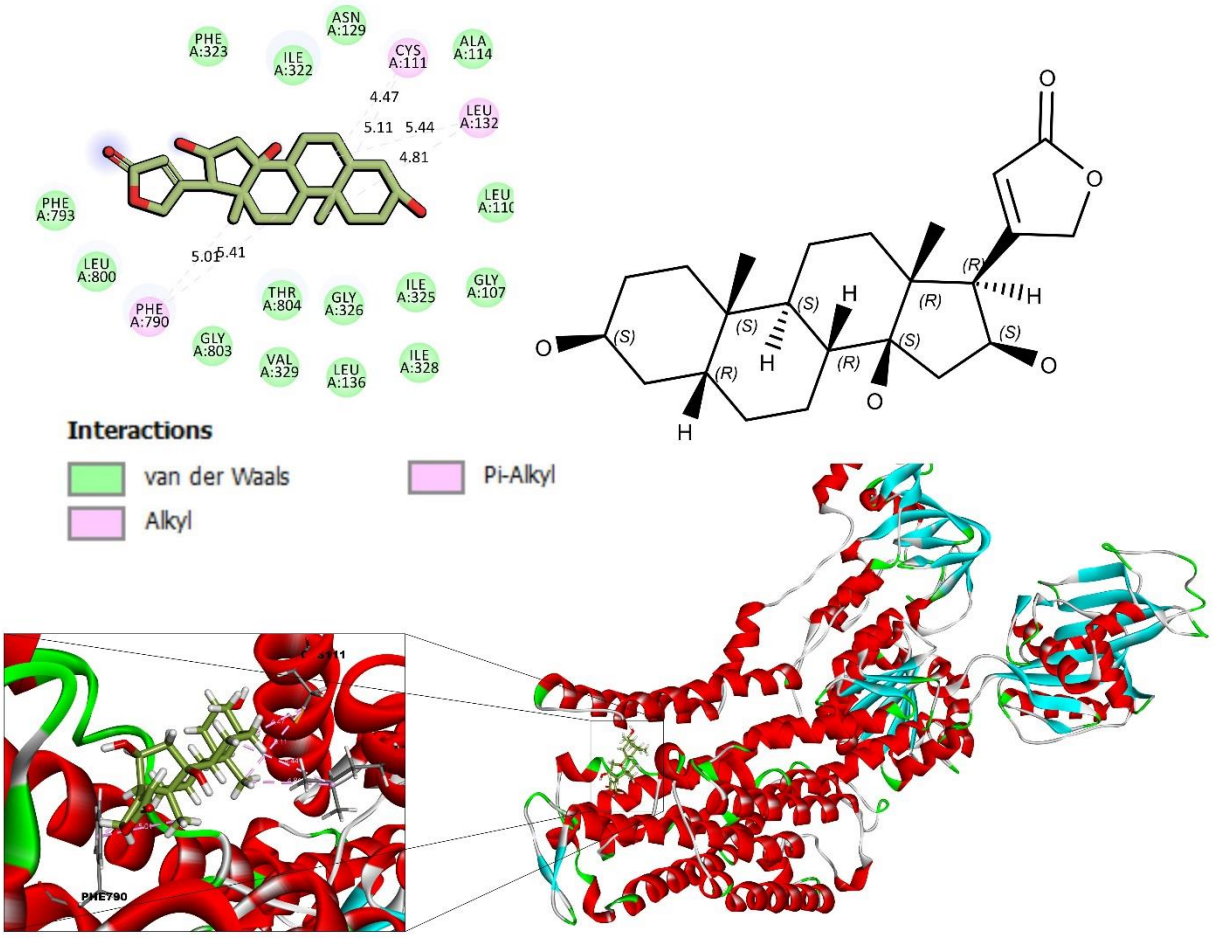

Figure S6 Docked pose of 3A3Y protein with ligand Gitoxigenin (Blue color) and Protein–ligand interaction maps developed from Accelrys Discovery studio visualizer 2016 (van der Waals-Light Green, conventional hydrogen bonds-Green color, carbon-hydrogen-White color, unfavourable donor-donor-Red color, π- sigma-Purple color, π- π T shaped-Dark pink color, alkyl and π- alkyl-Light Pink color)

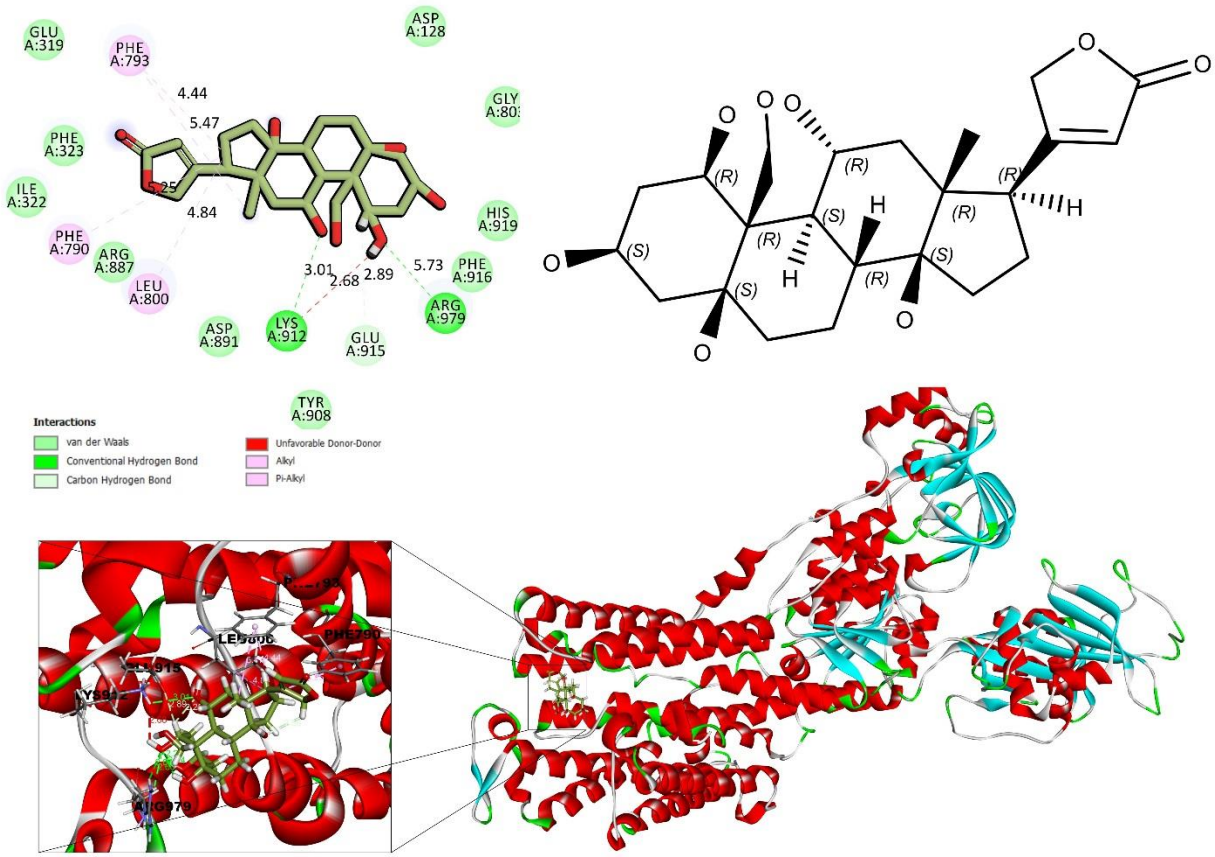

Figure S7 Docked pose of 3A3Y protein with ligand Ouabagenin (Blue color) docked pose and Protein– ligand interaction maps developed from Accelrys Discovery studio visualizer 2016 (van der Waals-Light Green, conventional hydrogen bonds-Green color, carbon-hydrogen-White color, unfavorable donor-donor-Red color, π- sigma-Purple color, π- π T shaped-Dark pink color, alkyl and π- alkyl-Light Pink color)

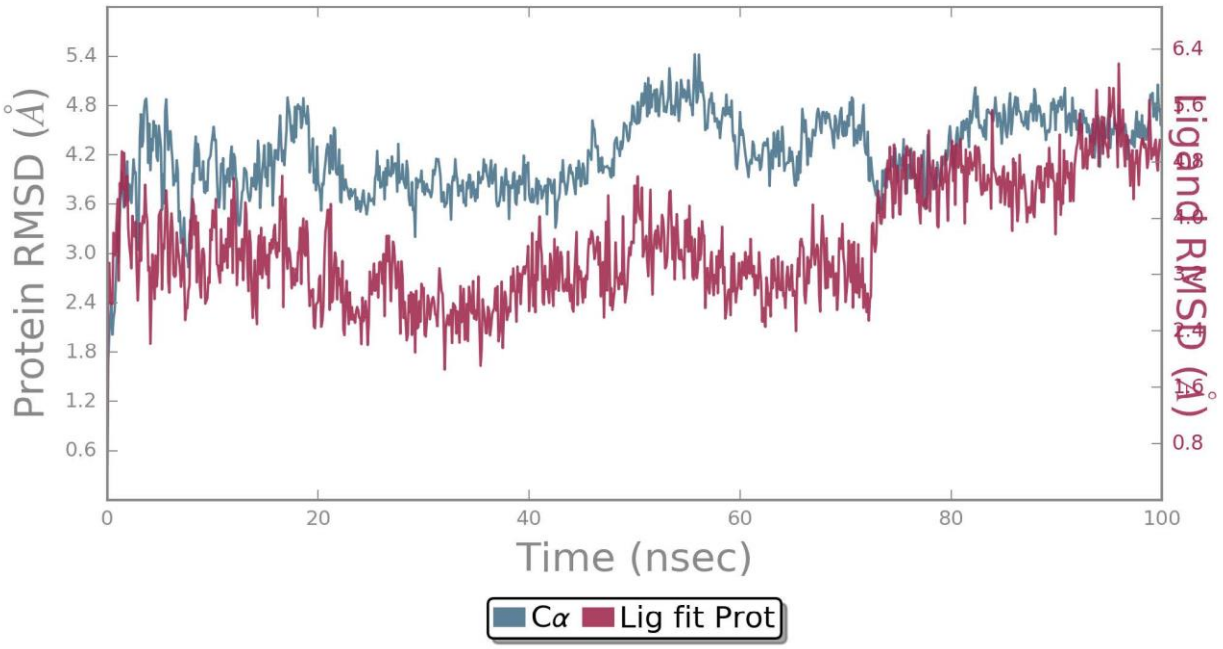

Figure S8 Protein- ligand RMSD analysis with residue index and Time level: Cα (blue color), side chains (green color), heavy atoms (yellow color), ligand with protein (dark pink color), ligand with ligand (pink color); Structure of the 3A3Y with Digoxigenin - Time against Protein RMSD

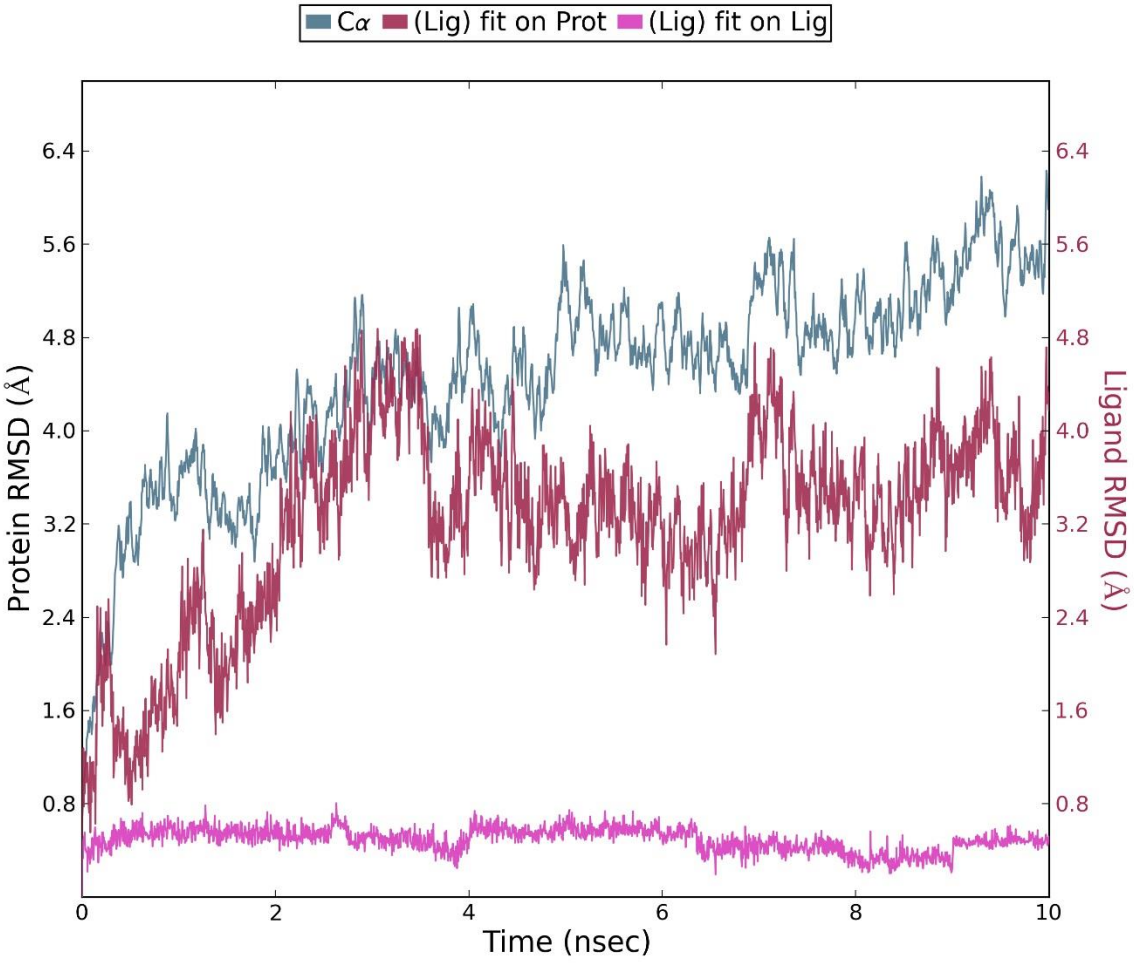

Figure S9 Protein- ligand RMSD analysis with residue index and Time level: Cα (blue color), side chains (green color), heavy atoms (yellow color), ligand with protein (dark pink color), ligand with ligand (pink color); Structure of the 3A3Y with Ouabain - Time against Protein RMSD

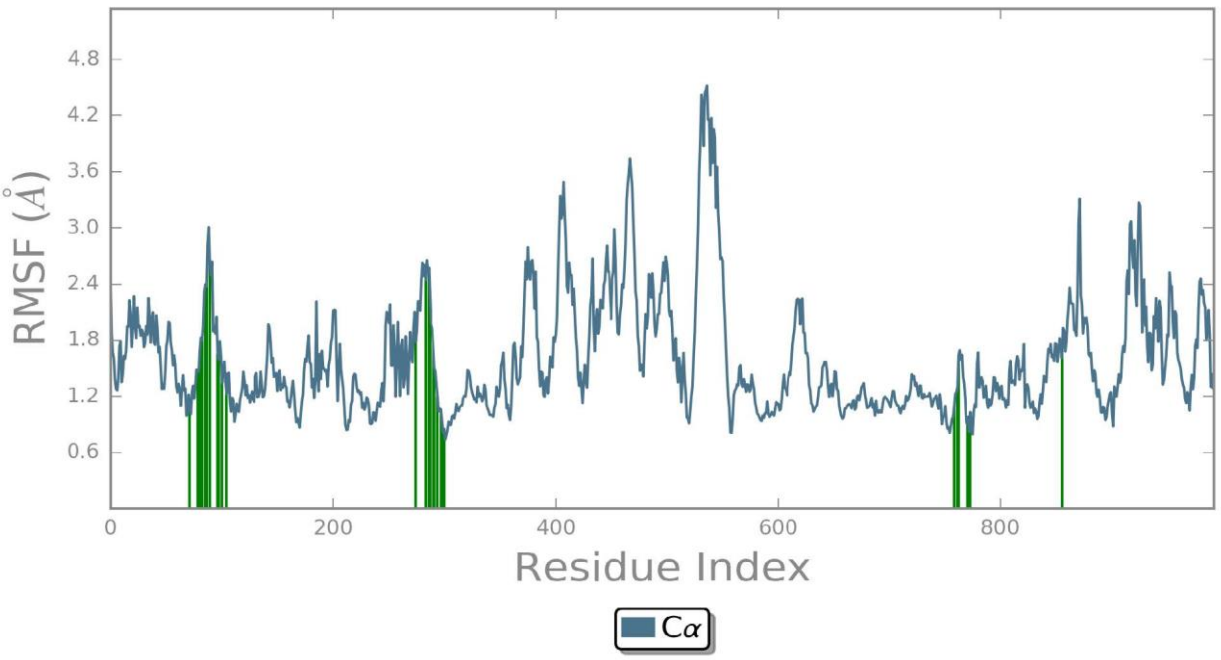

Figure S10 Protein- ligand RMSF analysis with residue index and Time level: Cα (blue color), side chains (green color), heavy atoms (yellow color), ligand with protein (dark pink color), ligand with ligand (pink color); Structure of the 3A3Y with Digoxigenin - Residue Index against RMSF

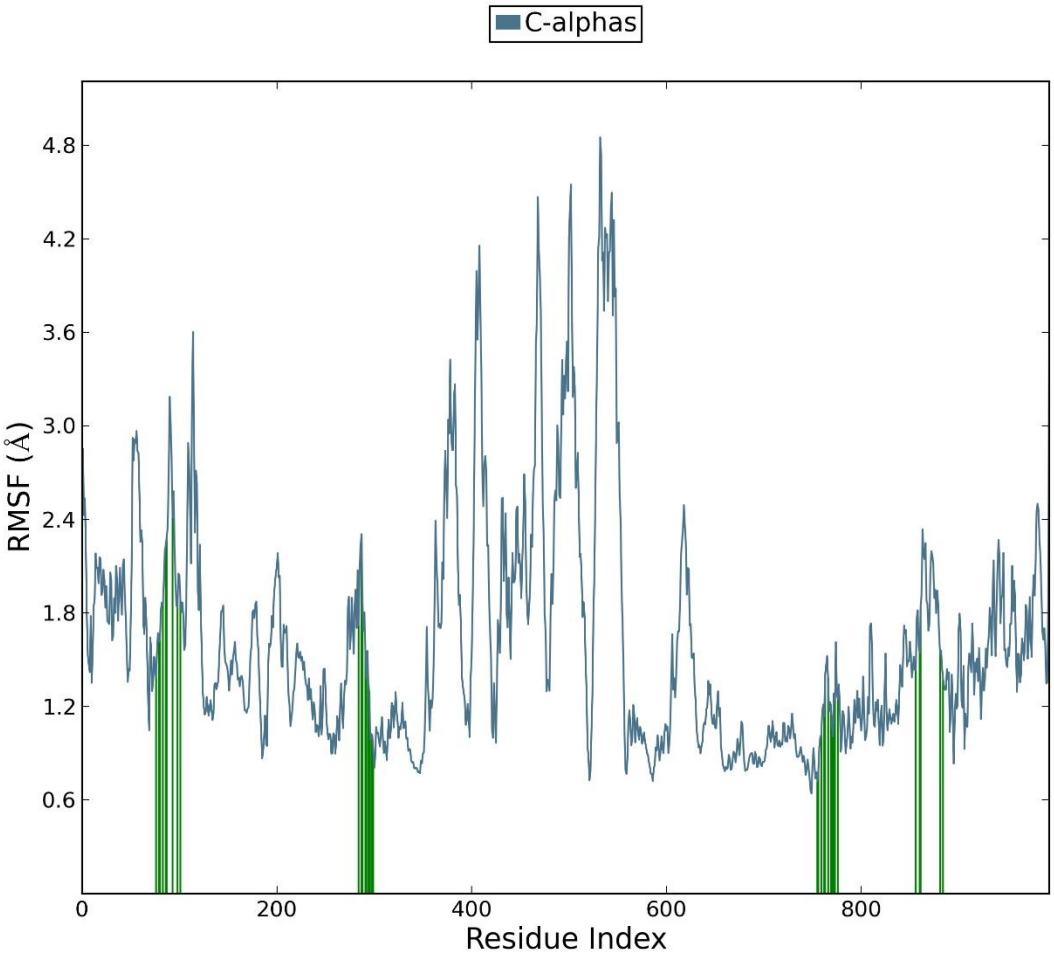

Figure S11 Protein- ligand RMSF analysis with residue index and Time level: Cα (blue color), side chains (green color), heavy atoms (yellow color), ligand with protein (dark pink color), ligand with ligand (pink color); Structure of the 3A3Y with Ouabain - Residue Index against RMSF

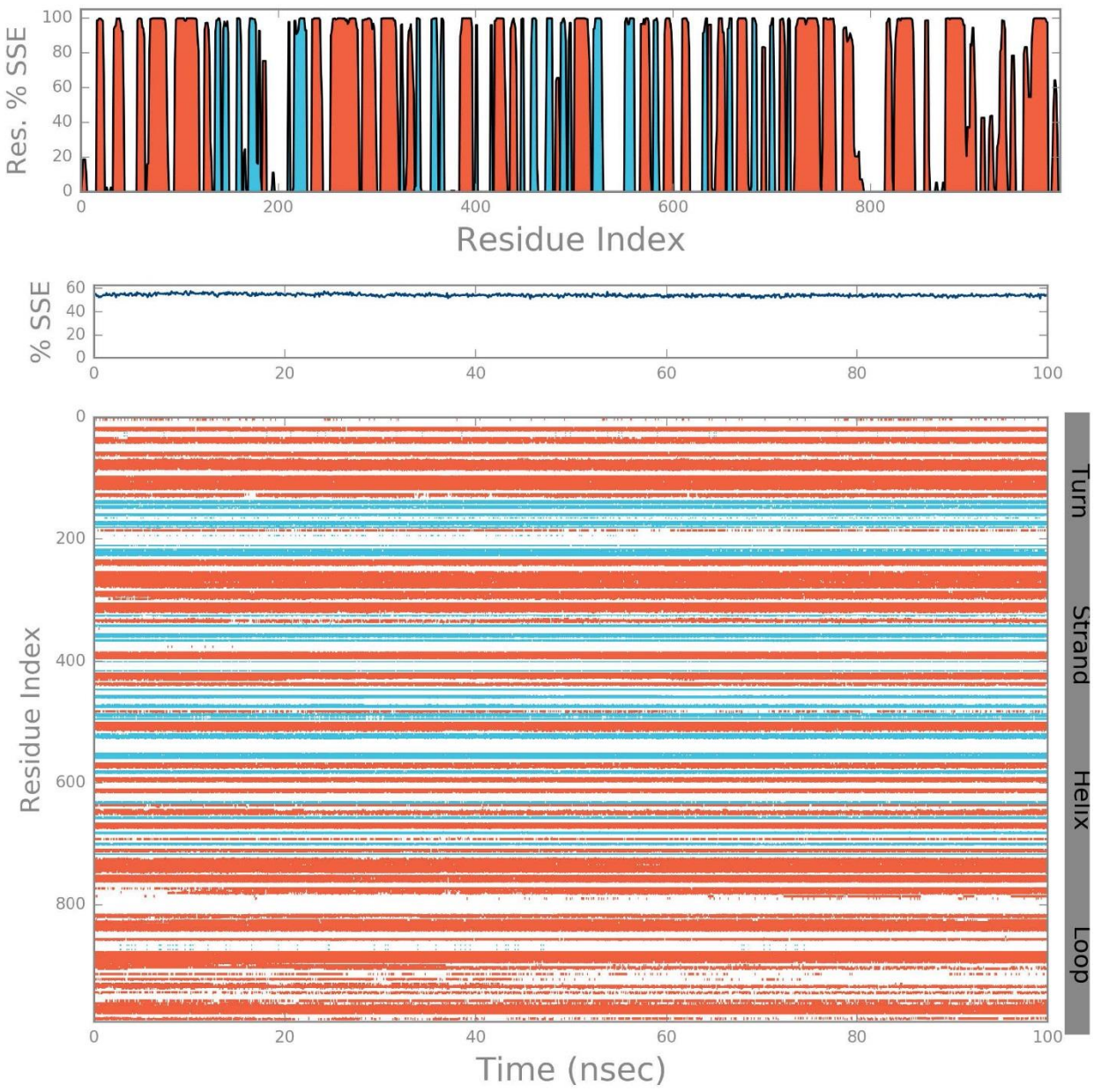

Figure S12 Protein Secondary Structure elements evaluation by Time (ns) vs. residue index and % SSE vs. residue index

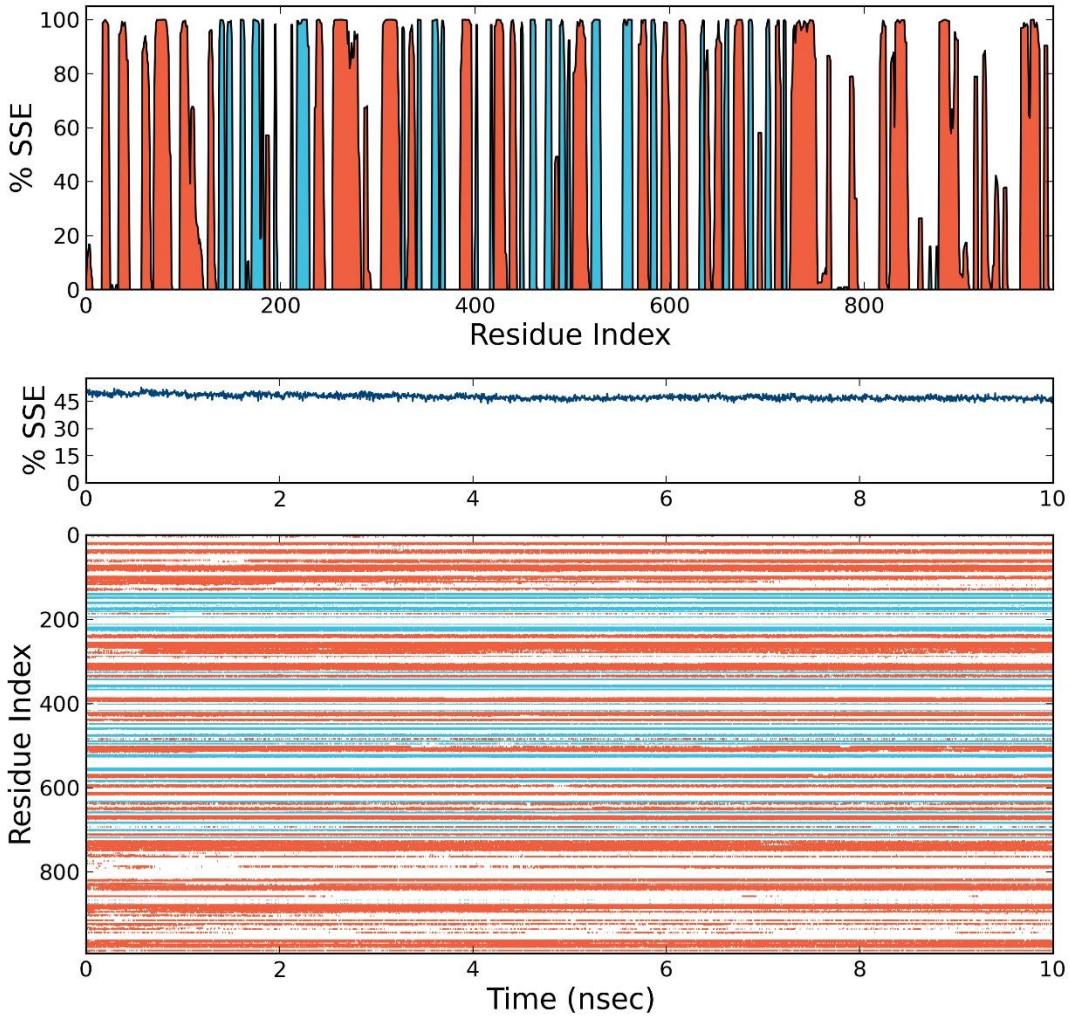

Figure S13 Protein Secondary Structure elements evaluation by Time (ns) vs. residue index and % SSE vs. residue index

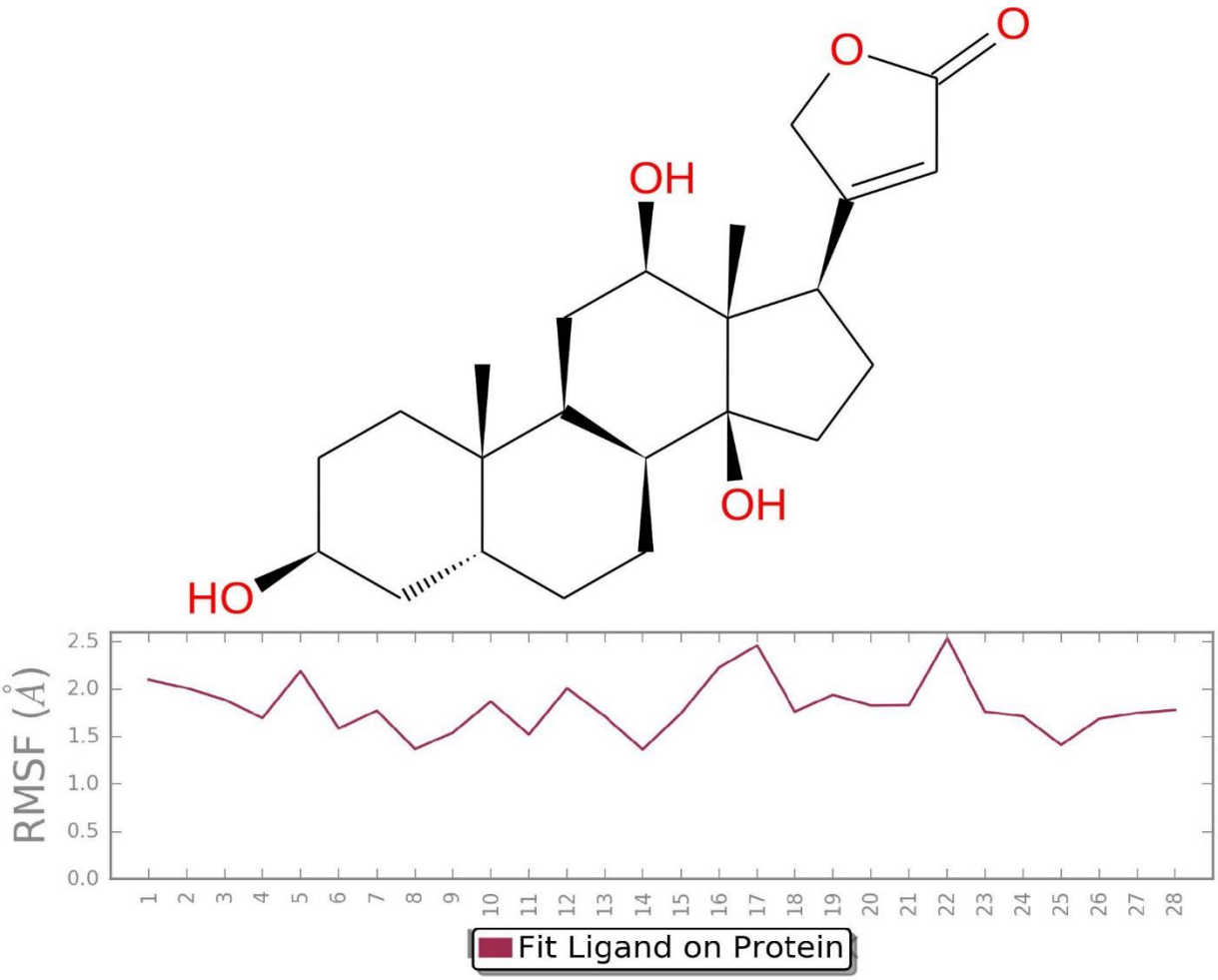

Figure S14 Digoxigenin RMSF arrangement: Fit on protein (Dark pink), Fit on ligand (Light pink)

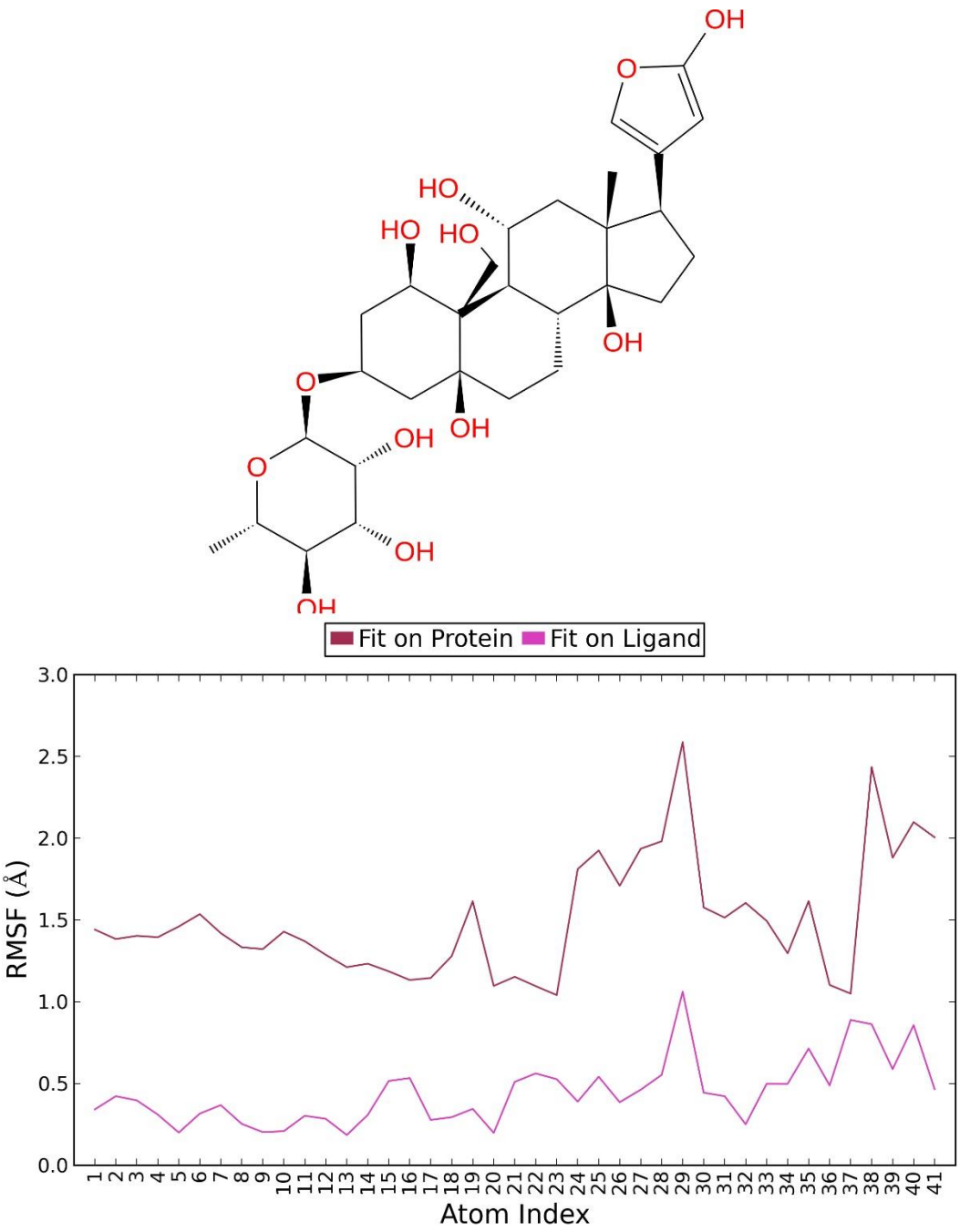

Figure S15 Ouabain RMSF arrangement: Fit on protein (Dark pink), Fit on ligand (Light pink)

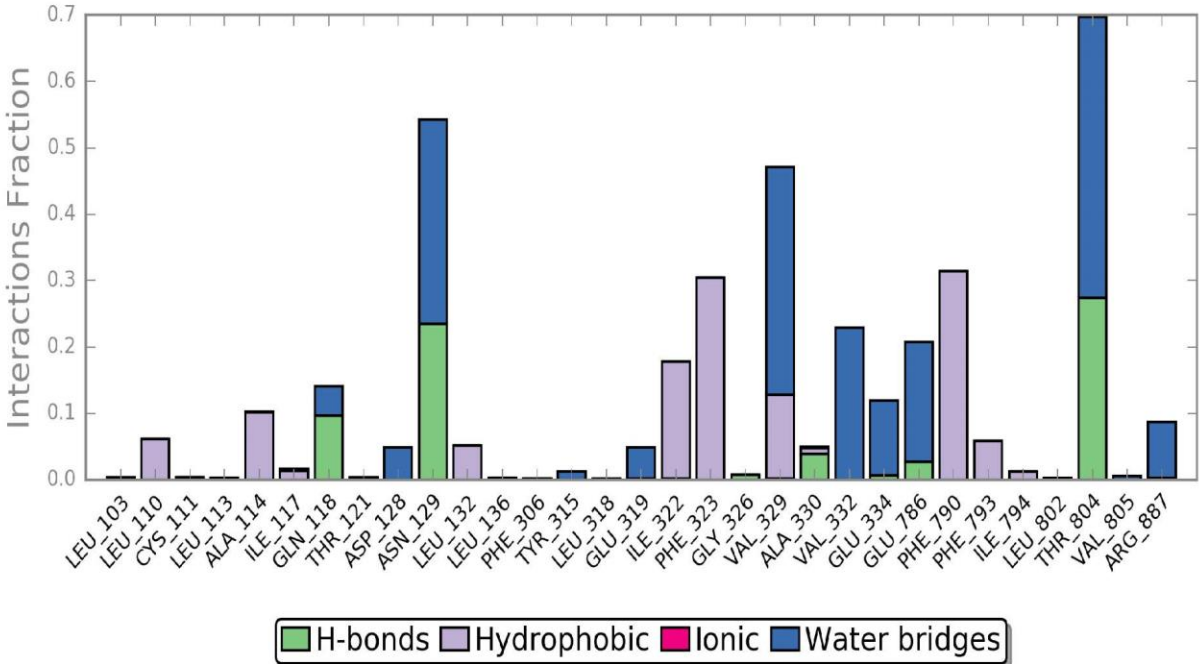

Figure S16 Protein- Digoxigenin Contacts Interpretation

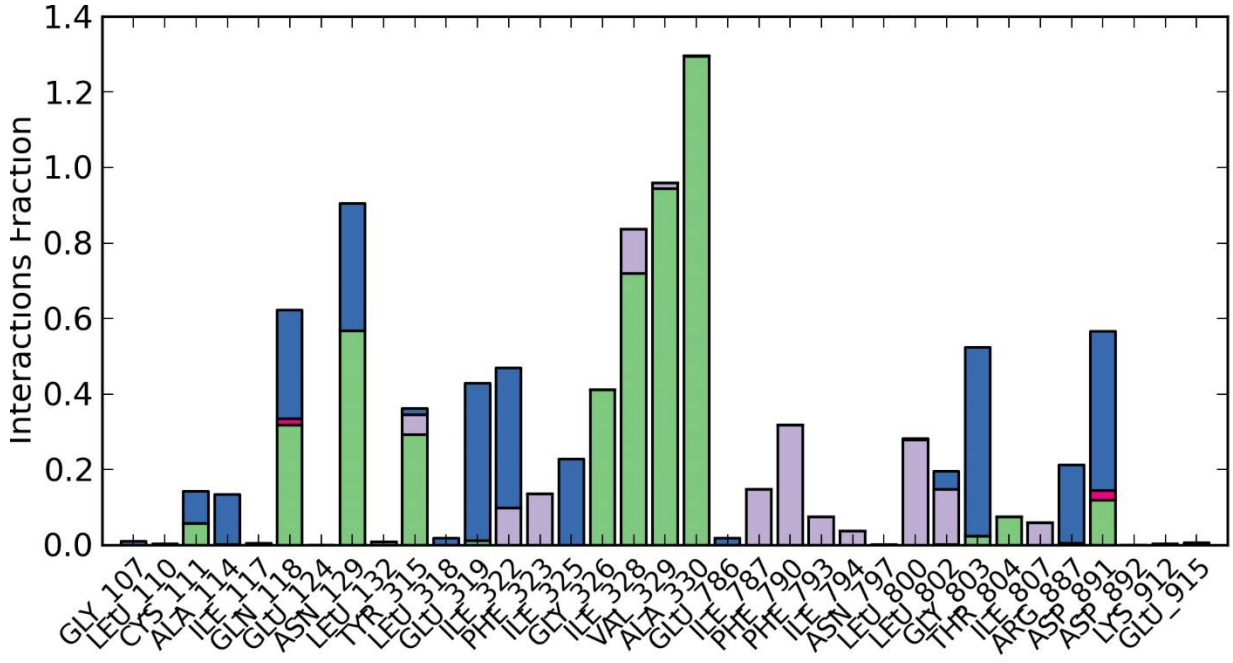

Figure S17 Protein- Ouabain Contacts Interpretation

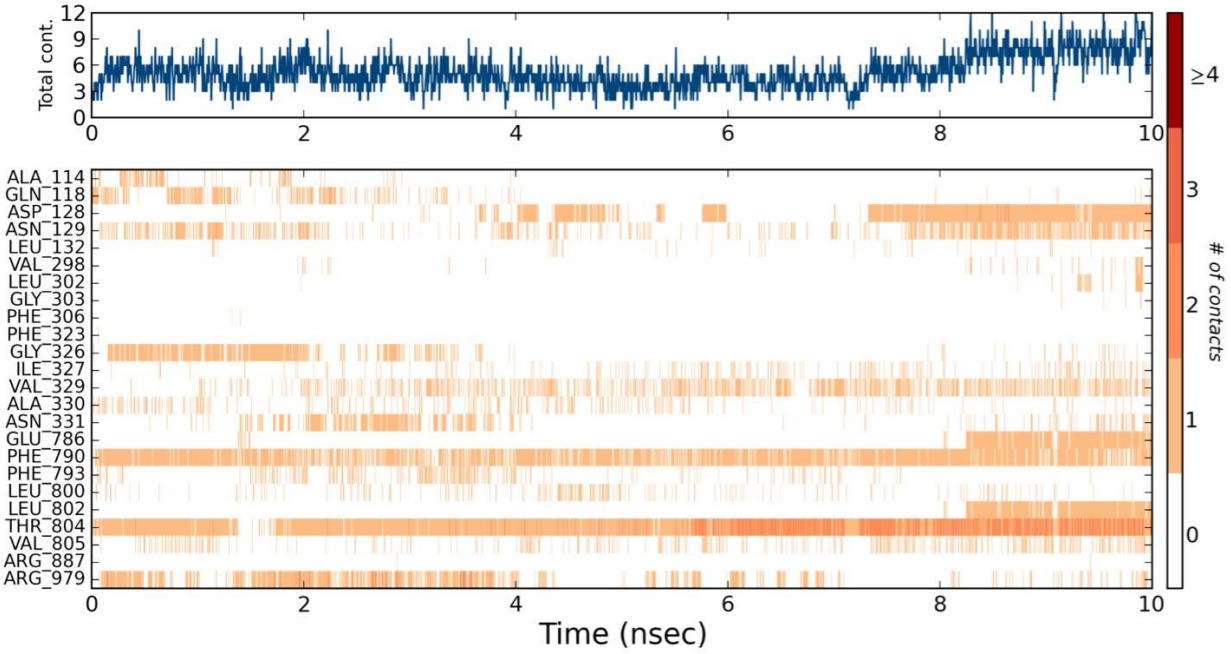

Figure S18 Interpretation of Protein- Digoxigenin Contacts by heat map

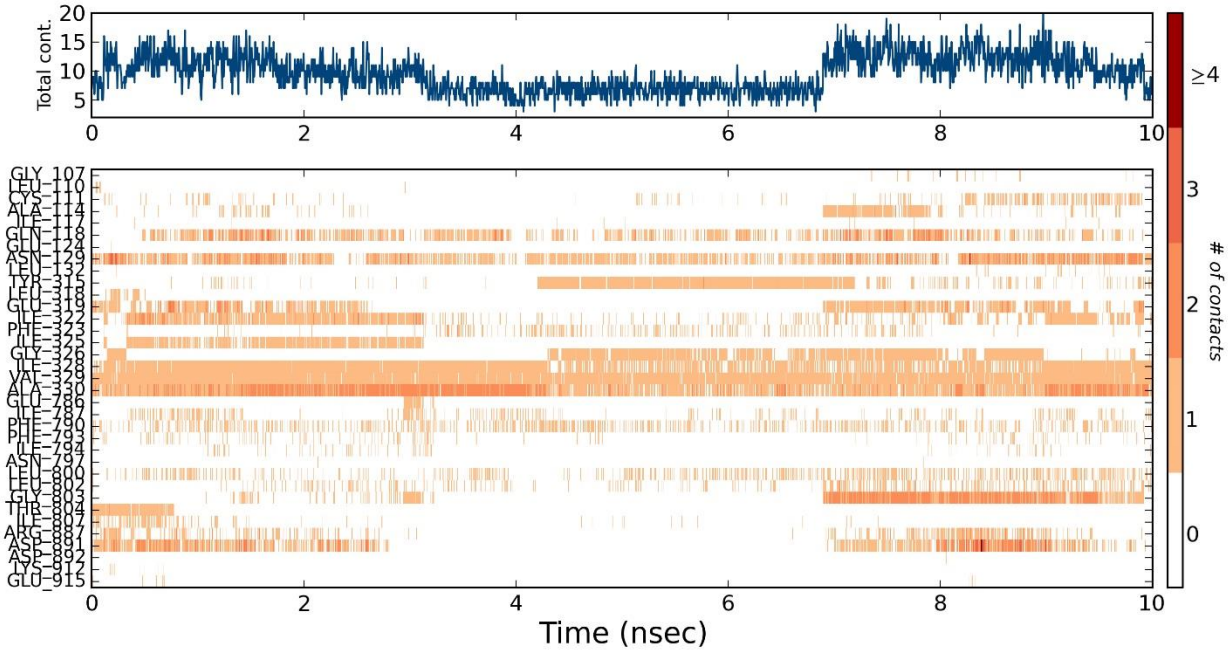

Figure S19 Interpretation of Protein- Ouabain Contacts by heat map

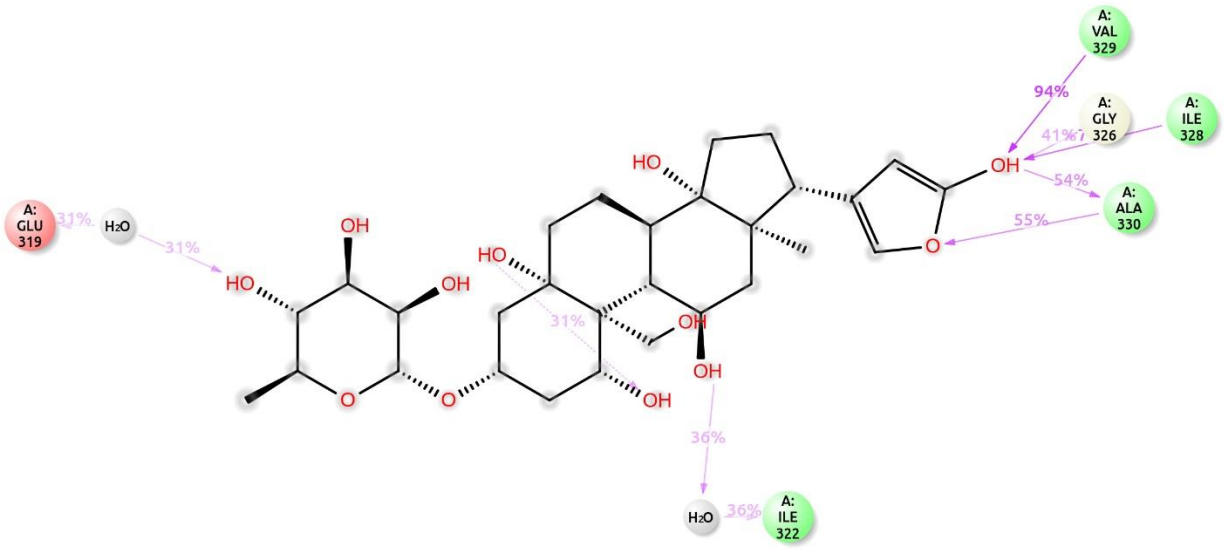

Figure S20 Interpretation of Digoxigenin -Protein Conserved Contacts

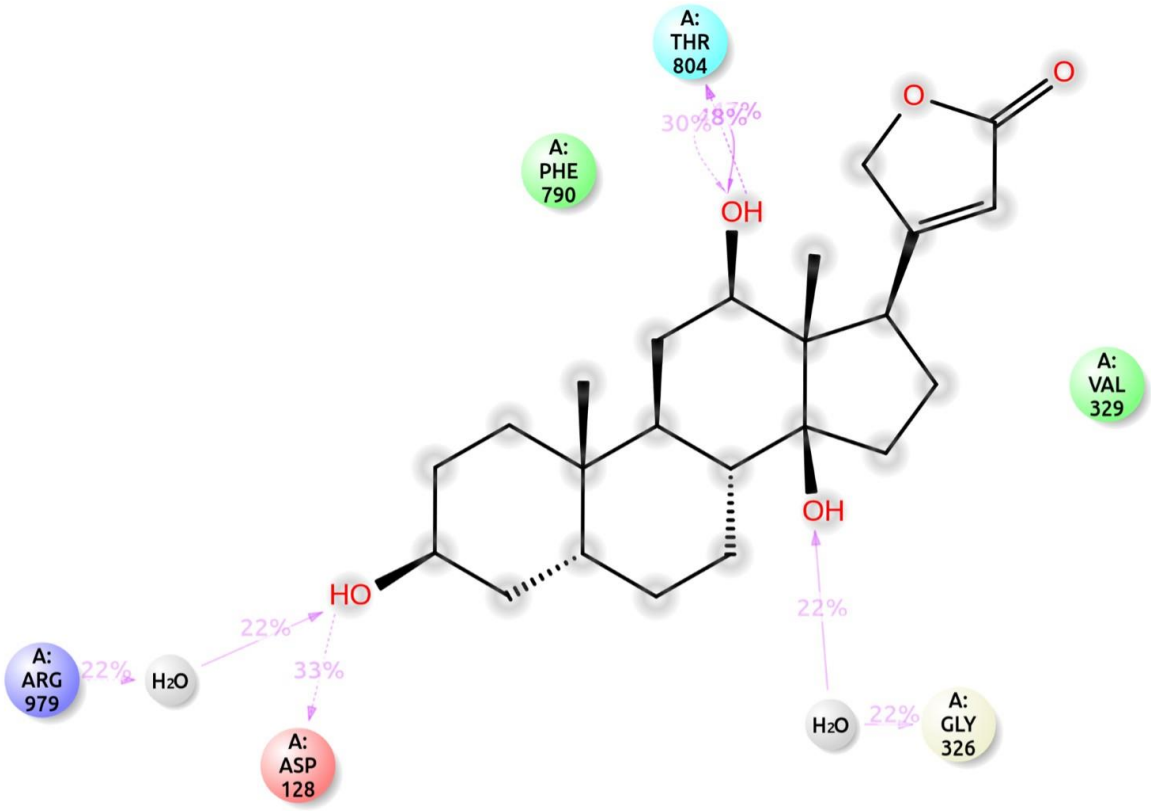

Figure S21 Interpretation of Ouabain -Protein Conserved Contacts

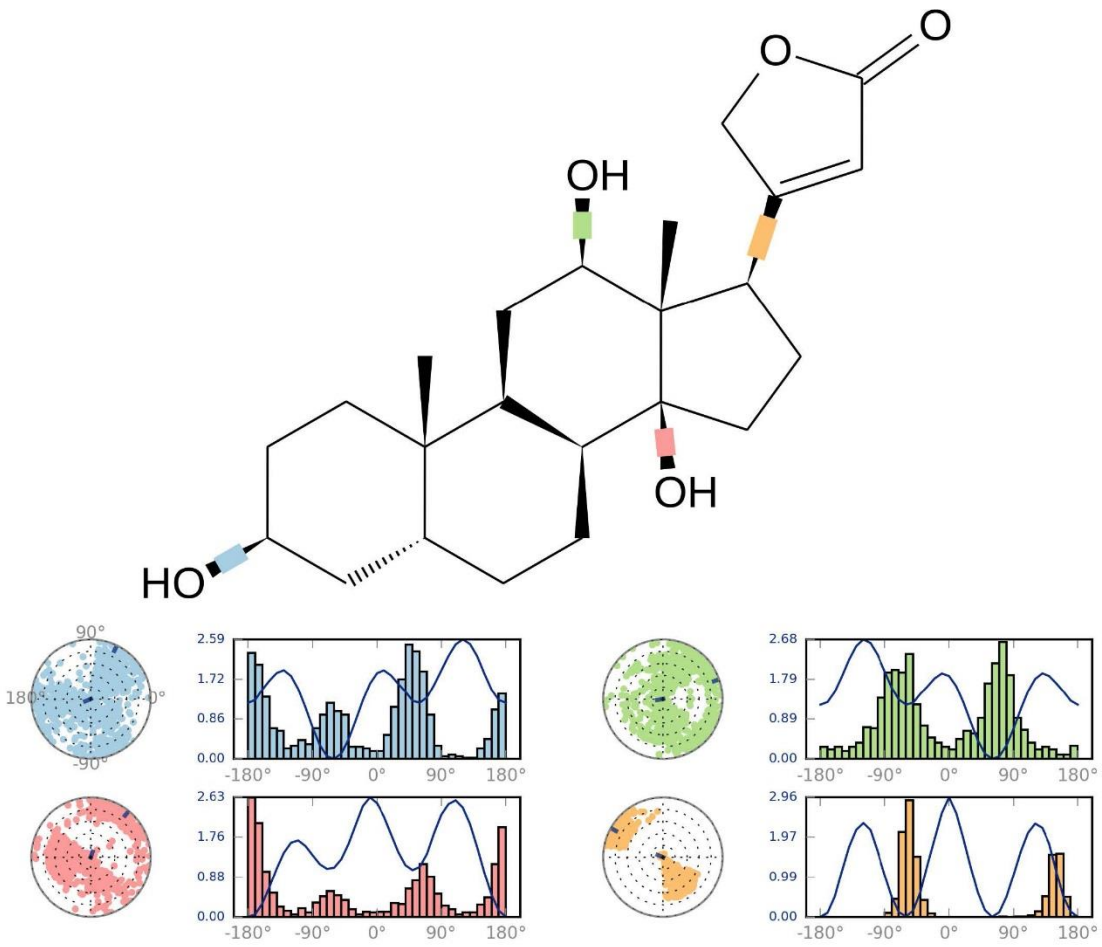

Figure S22 Torsional profiles of Receptor-Digoxigenin complex

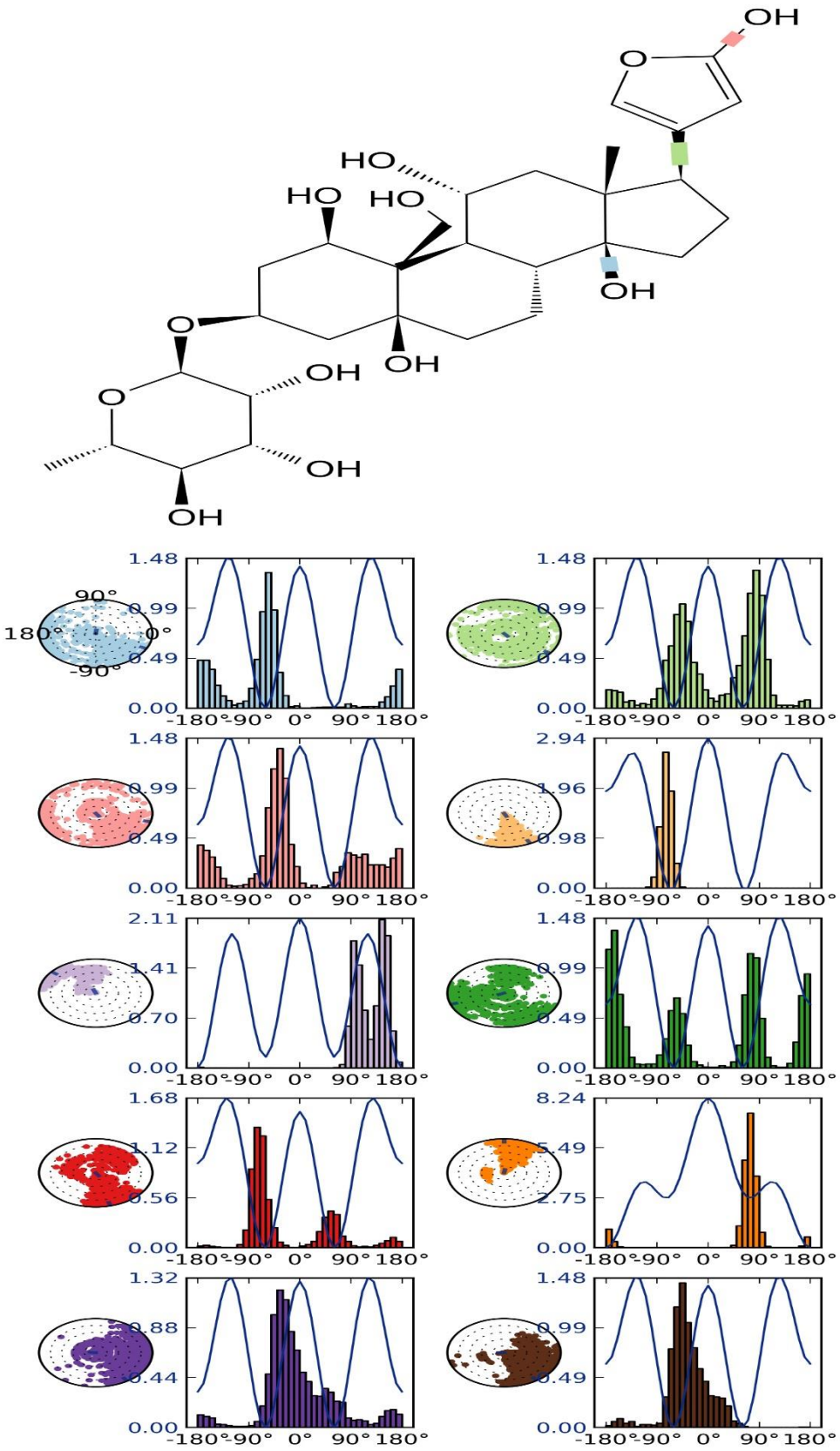

Figure S23 Torsional profiles of Receptor- Ouabain complex