From Tapinarof to Novel AhR Modulators: Computational Drug Discovery for Psoriasis Therapeutics

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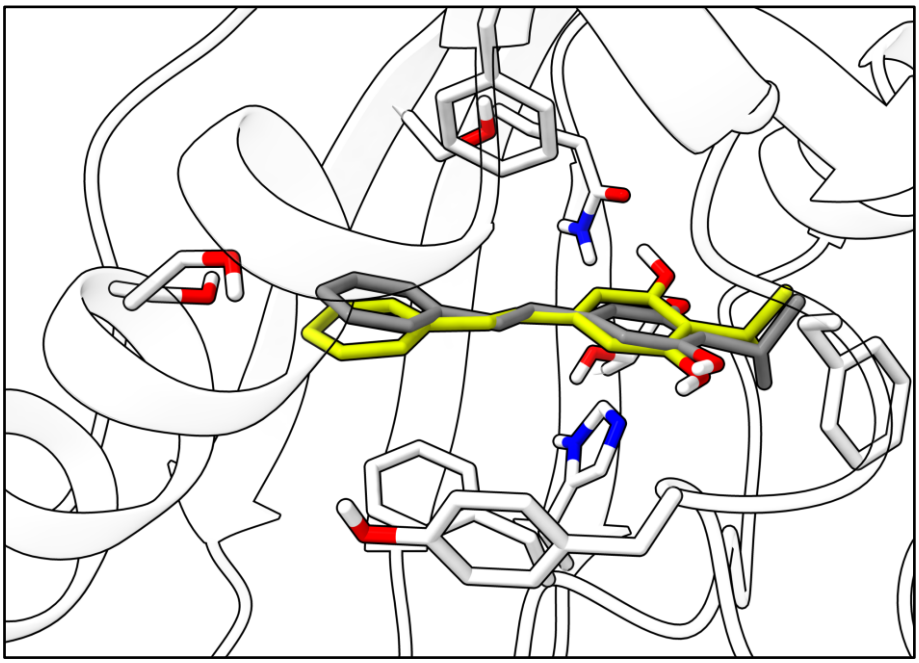
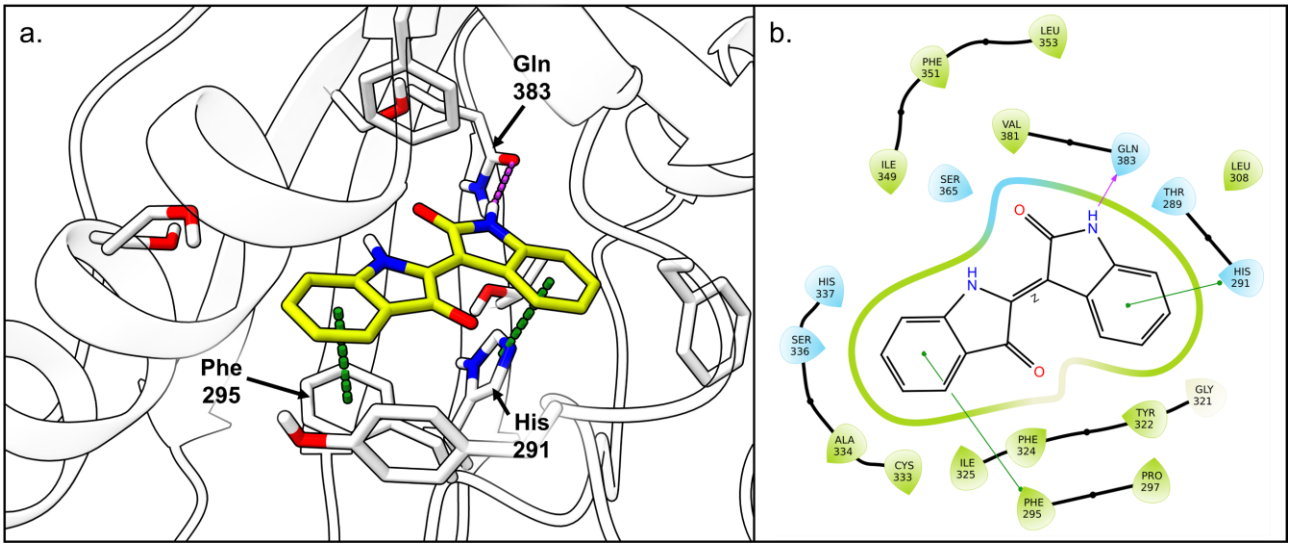
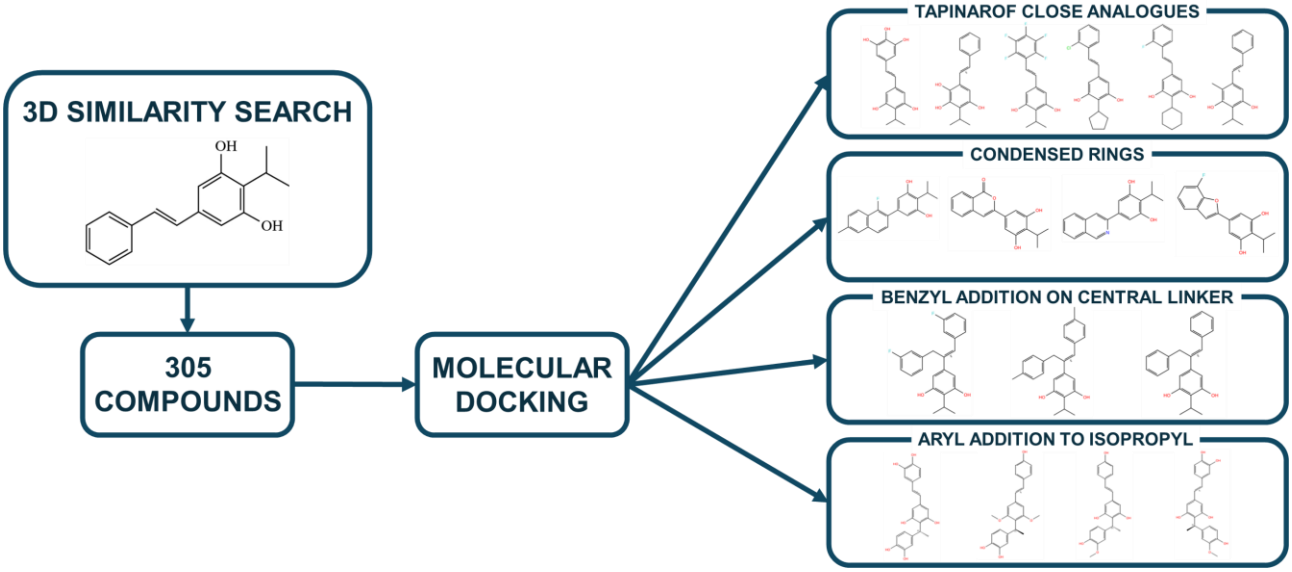
Supplementary Information



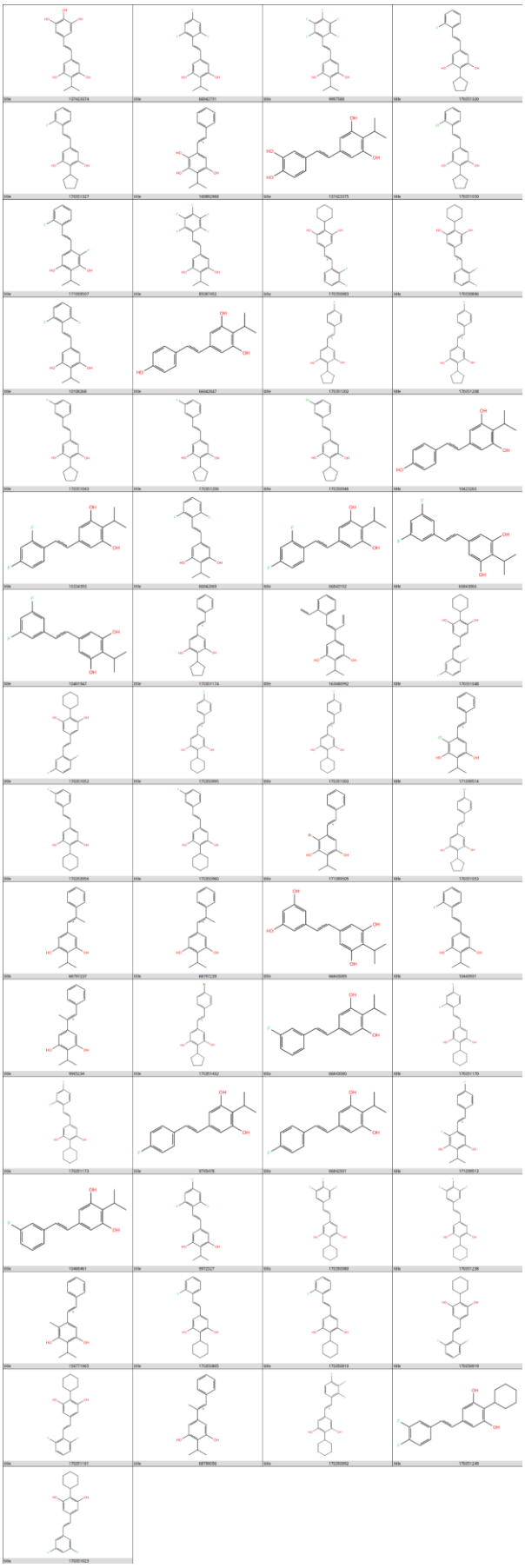
Supplementary Figure 1: Comparison of the tapinarof experimental binding mode (grey sticks) in the porcine AhR X-ray structure (PDBID: 8XS6) with the binding pose predicted by docking (yellow sticks).



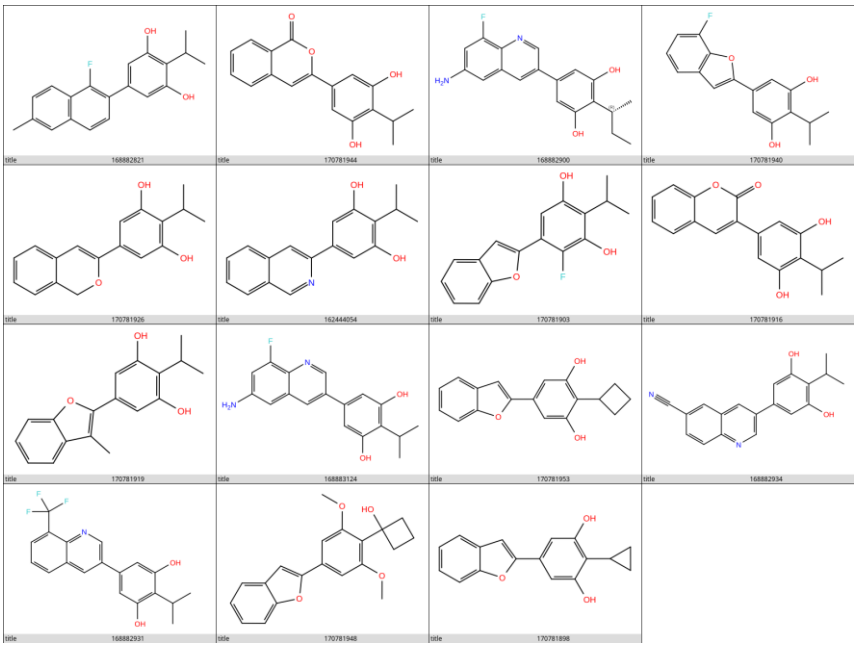
Supplementary Figure 2: Experimental binding mode of the indirubin molecule within the AhR PAS-B domain (PDBID 7ZUB). a. 3D representation of the binding pose: indirubin is depicted in yellow sticks; protein is shown as white cartoon; relevant residues are represented in white sticks; π-stacking interactions are shown with green dashed lines; H-bonds are represented as magenta dashed lines. b. 2D representation of the indirubin interactions.



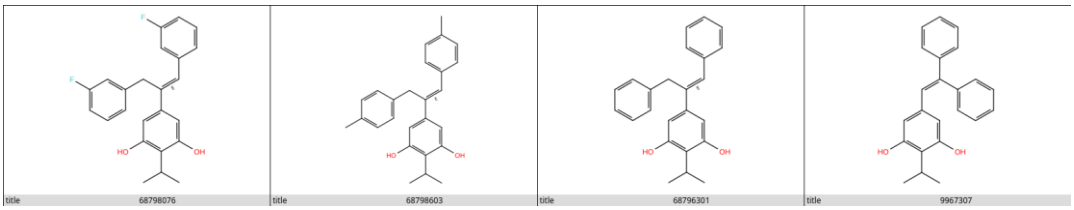
Supplementary Figure 3: Scheme for the first step of the multi-stage search strategy in PubChem: 3D Similarity search using tapinarof as query molecule.



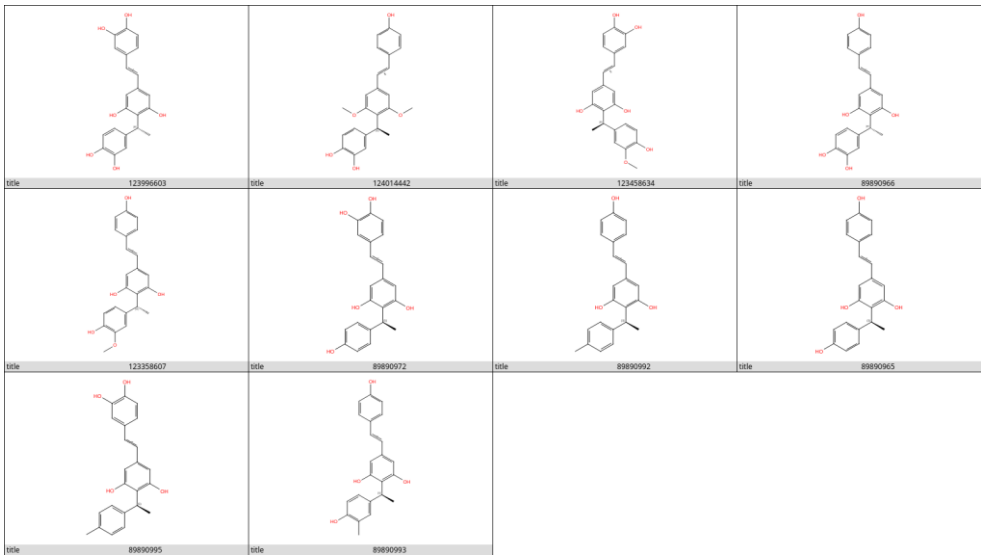
Supplementary Figure 4: Chemical structures of the “tapinarof close analogues” compounds.



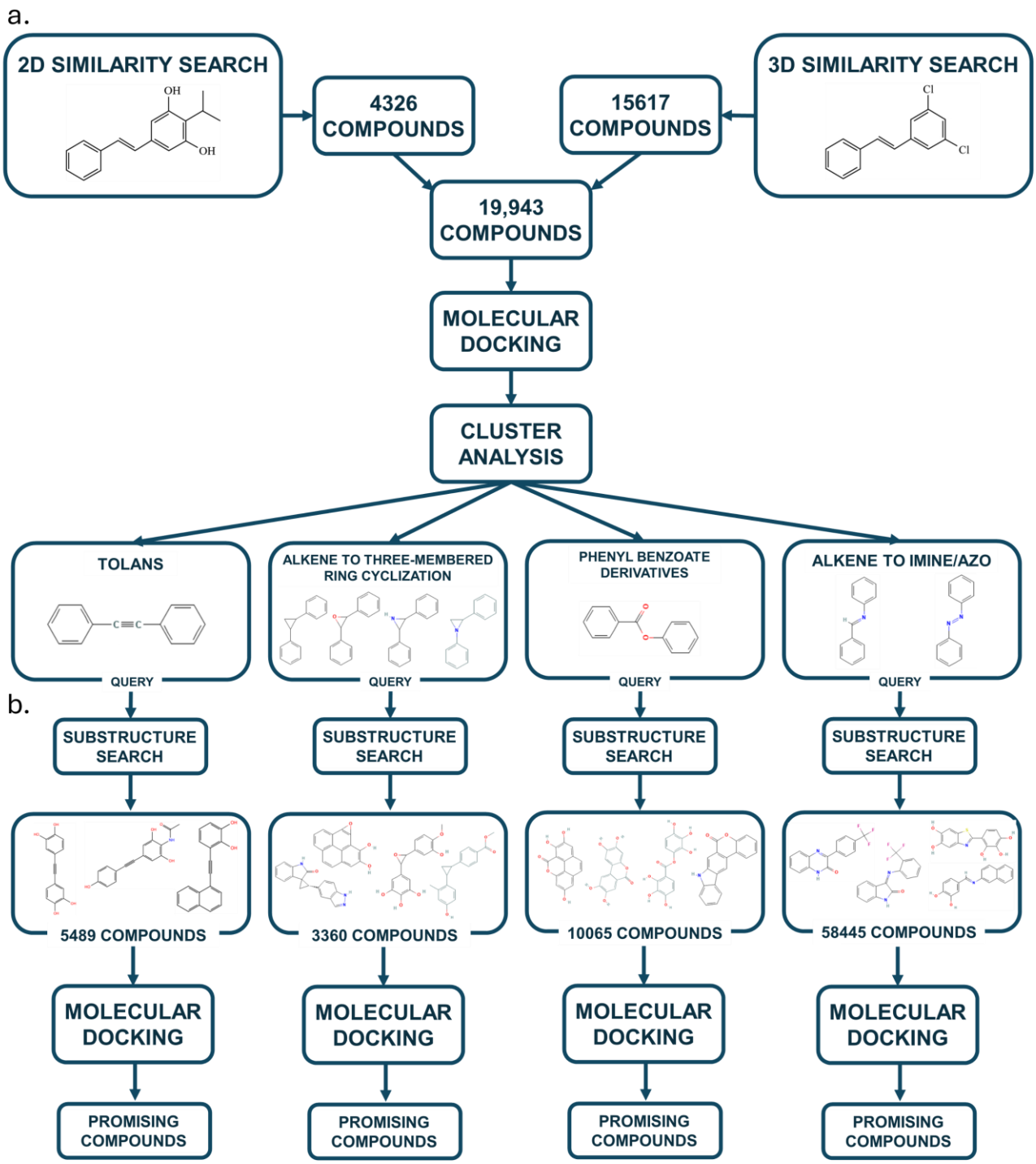
Supplementary Figure 5: Chemical structures of the “condensed rings” compounds.



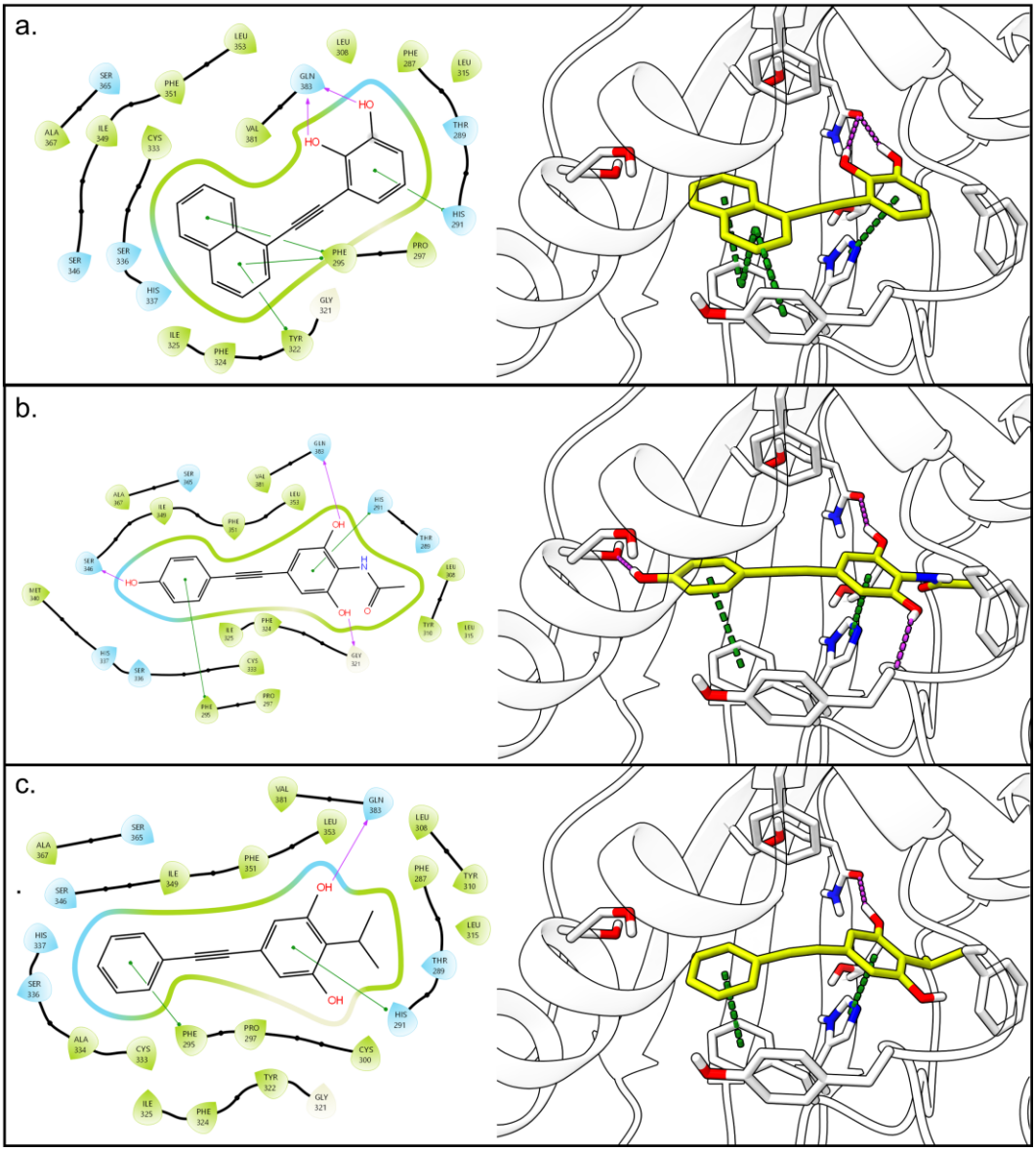
Supplementary Figure 6: Chemical structures of the “benzyl addition on central linker” compounds.



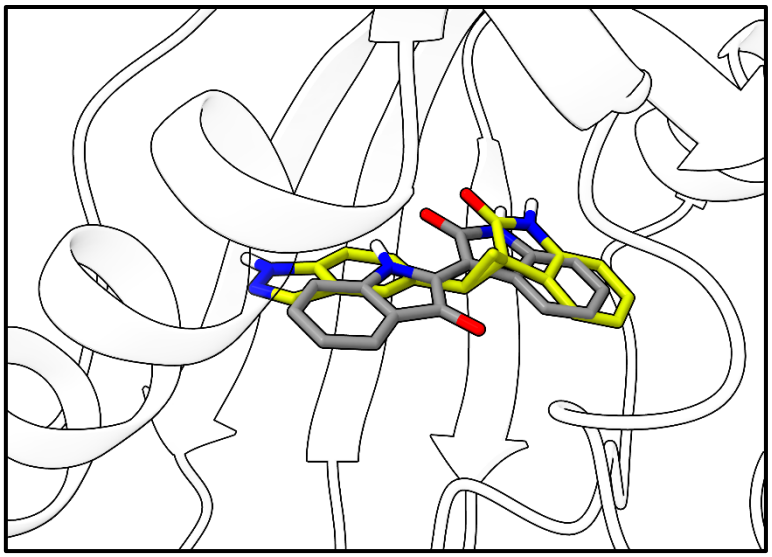
Supplementary Figure 7: Chemical structures of the “aryl addition to isopropyl” compounds.



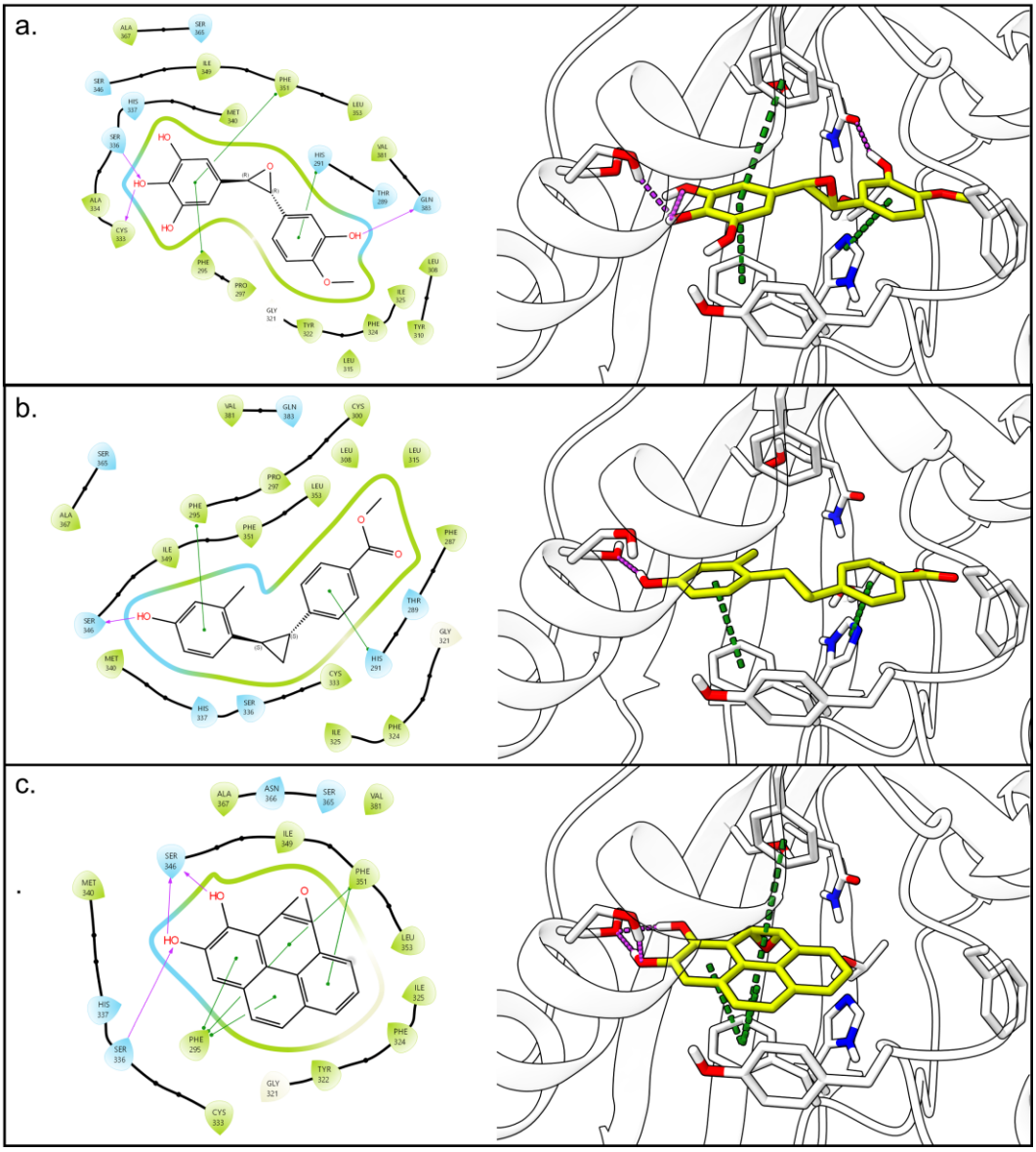
Supplementary Figure 8: Scheme for the second and third step of the multi-stage search strategy in PubChem: a. 2D Similarity search using tapinarof as query molecule and 3D similarity search using 1,3-dichloro-5-(2-phenylethenyl)benzene as query molecule. b. Expansion of the search on the most promising families of compounds using substructure search.



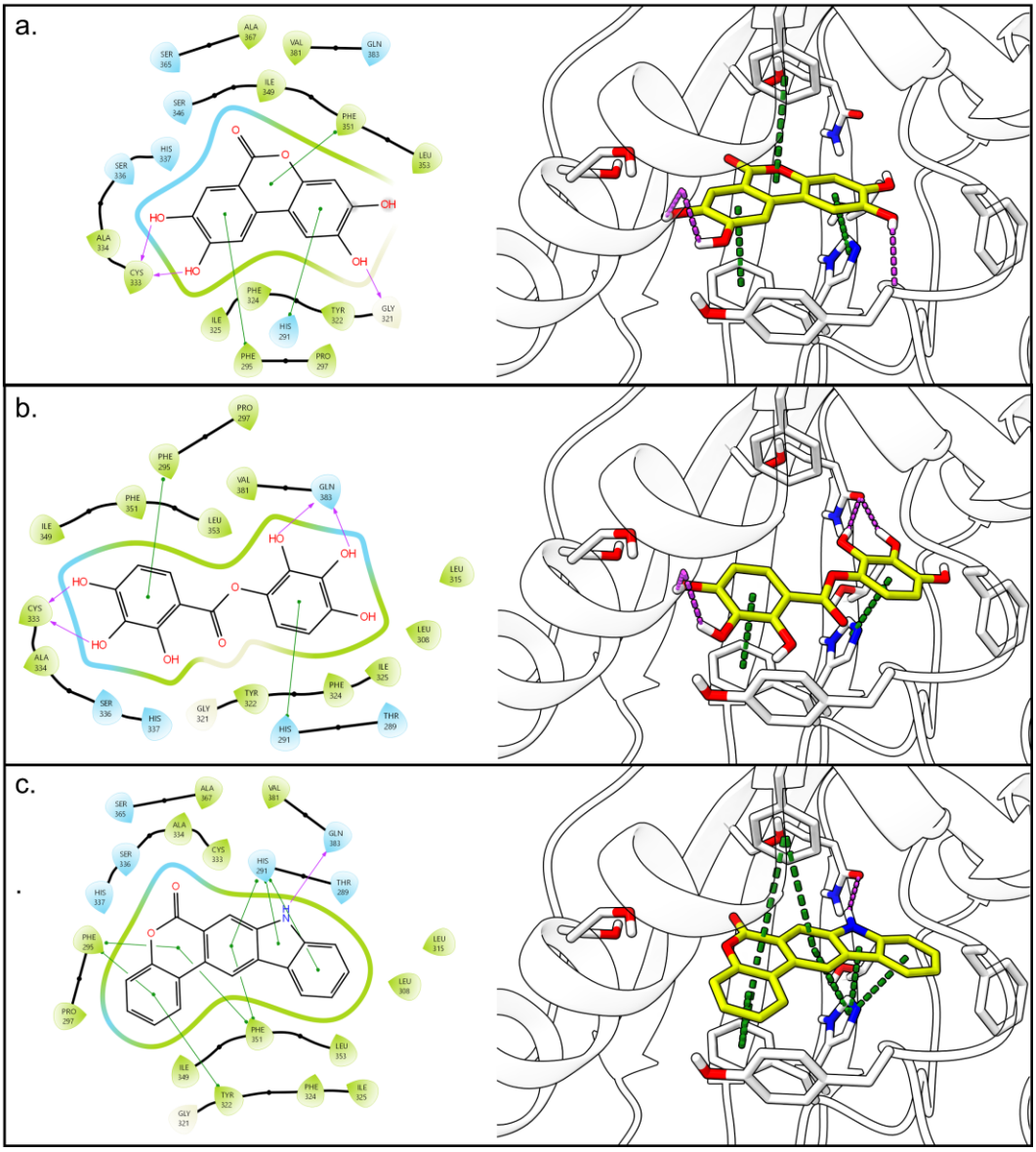
Supplementary Figure 9: Binding modes of representative compounds from the tolan family: (a) A tolan with fused rings; (b) A tolan that preserves all the interactions present in the tapinarof binding mode; (c) The exact tapinarof analogue. 2D representation of the ligand interactions are shown in the left panels, while 3D representations of the binding pose are shown in the right panels.



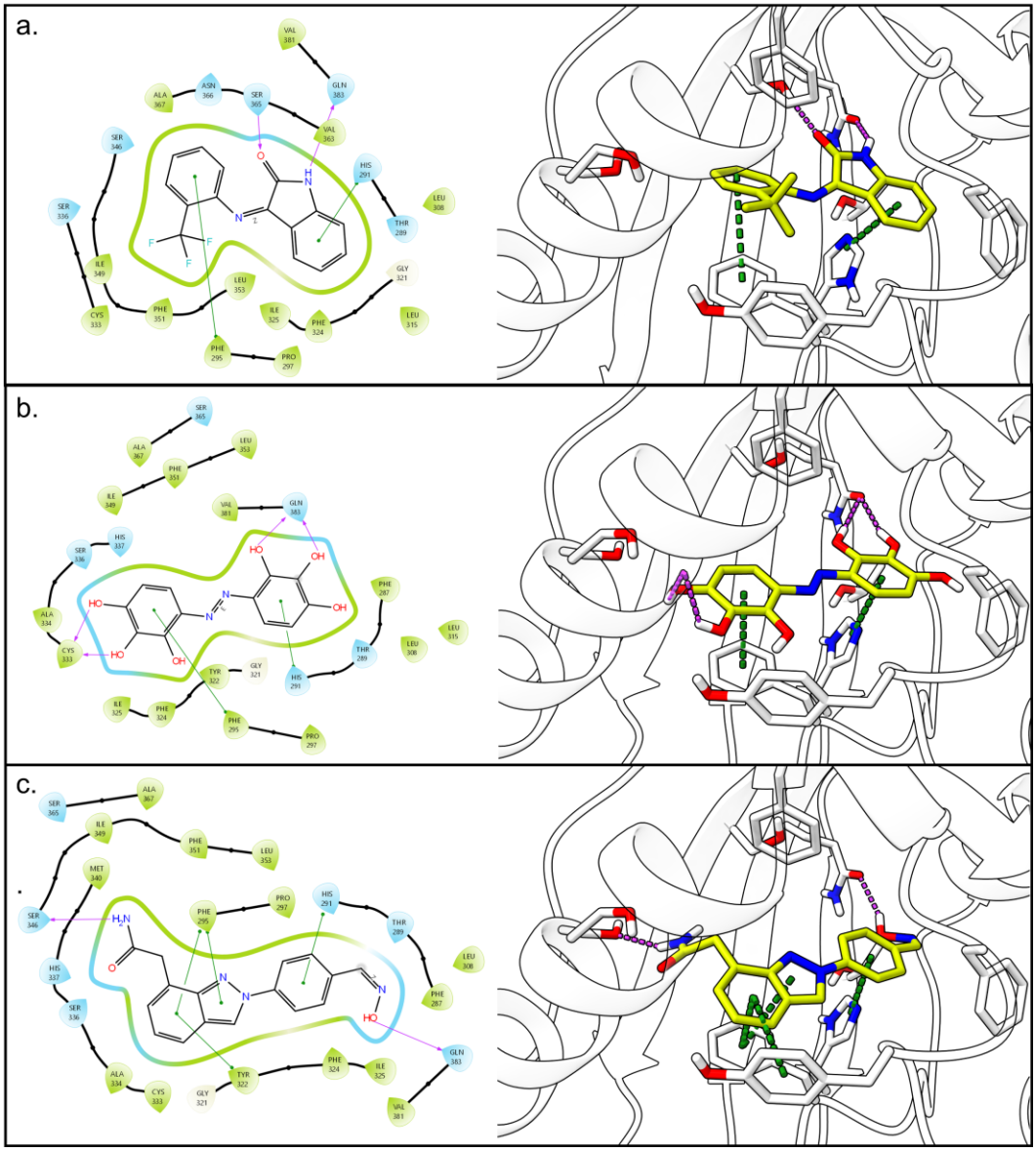
Supplementary Figure 10: Comparison of the experimental binding mode of indirubin (gray sticks, PDB ID: 7ZUB) with the docking-predicted binding pose of the best ligand from the 'alkene to three-membered ring cyclization' family (yellow sticks).



Supplementary Figure 11: Binding modes of representative compounds from the 'alkene to three-membered ring cyclization' family: (a) A stilbene that has undergone epoxidation at the central alkene; (b) A stilbene in which the central alkene has been replaced by a cyclopropane; (c) A compound consisting of four fused rings. 2D representation of the ligand interactions are shown in the left panels, while 3D representations of the binding pose are shown in the right panels.



Supplementary Figure 12: Binding modes of representative compounds from the 'phenyl benzoate derivatives' family: (a) A compound in which the ester group forms a fused unsaturated lactone ring; (b) A compound with an open-chain phenyl benzoate scaffold; (c) A compound with five fused aromatic rings. 2D representation of the ligand interactions are shown in the left panels, while 3D representations of the binding pose are shown in the right panels.



Supplementary Figure 13: Binding mode of some representative compounds found within the "alkene to imine/azo" family. a. A compound presenting an indol-2-one ring; b. An azo derivative of hydroxy-stilbene (azobenzene); c. A compound containing an indazole ring and two polar groups at the opposite ends forming H-bonds. 2D representation of the ligand interactions are shown in the left panels, while 3D representations of the binding pose are shown in the right panels.