**Results**

2.4 [*Molecular docking of compounds* ***4n****,* ***8f*** *and* ***4a*** *to LXRα*

We docked 2 active compounds, i.e., **4n** and **8f**, and one inactive compound **4a** against LXRα by smina (Figure 4). The re-docking of the crystal ligand reproduced crystallographic poses (Figure 4D), which implied that the chosen docking parameters were suitable. The docking scores of **4n** and **8f** were -8.13 and -10.47 Kcal/mol, while the docked ligand was -12.46 Kcal/mol, implying that **4n** and **8f** could bind to LXRα with lower binding affinity compared to the crystal ligand. **4n** and **8f** resided in a hydrophobic sub-pocket composed of M134, F151, F93 and L167 (Figure 4A&B). In addition, **4n** and **8f** could form hydrogen bonds with T138. Although the inactive compound **4a** had a docking score of -8.77 Kcal/mol, it bound to a different sub-pocket from **4n** and **8f** (Figure 4A, B & C) and **4a** formed a hydrogen bond with H257.



**Figure. 4**: **The docking mode of compound 4n, 8f and 4a against LXRα.** LXRα (PDB ID: 5HJS) is shown in gray cartoon, essential residues in gray sticks, compounds **4n** (A), **8f** (B), **4a** (C) and docked ligand (D) in yellow sticks. The crystal ligand (D) is shown in green sticks. The polar interactions between the compounds and LXRα are shown in black dashes and labled in Å.

**Methods**

**Molecular docking.**

There are 7 crystal LXRα structures in protein data bank (PDB), i.e., PDB ID: 1UHL, 3IPQ, 3IPS, 3IPU, 5AVI, 5AVL, and 5HJS. 5HJS, with the highest resolution, 1.72 Å, was chosen for docking. Compounds **4n**, **8f** and **4a** were docked to LXRα by smina,1 which is a fork of AutoDock Vina2. All compounds were pre-processed by the Ligprep in Schrödinger 2020 (Schrödinger LLC, New York, NY, USA), with Epik to generate the proper protonation states at pH 7.0. Only chain A of the 5HJS was used for docking, crystal ligand was preserved and all the water molecules were dropped. The crystal ligand was used to define the grid with the parameter --autobox\_ligand. The random seed was explicitly set to 0 and all other docking parameters were set as default. For each compound, the docking conformation with the best docking score was chosen for further analysis.

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2. Oleg Trott, Arthur J. Olson, AutoDock Vina: Improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading. *J. Comput. Chem.* **2010,** *31* (2), 455-461.