

Structure-Guided Docking of WEA001, a Goldilocks ER α Antagonist for Endocrine-Resistant Breast Cancer

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Abstract

Endocrine resistance in estrogen receptor alpha (ER α)-positive breast cancer is associated with persistent receptor signaling and ligand-binding-domain mutations, including L536S and Y537S, for which no current antagonist reliably restores receptor inactivation. WEA001 was independently designed as a Goldilocks ER α antagonist candidate that combines an estradiol-like core with a structured, helix 12 (H12)-directed tail. We hypothesized that WEA001 would preferentially generate favorable docking poses in wild-type and resistance-associated ER α conformations while failing to yield a comparably stable pose in the agonist-state estradiol-bound model.

Estradiol-bound 1A52, 4-hydroxytamoxifen-bound 3ERT, fulvestrant-bound L536S 6SBO, and Y537S 6CHZ ER α structures were prepared in Schrödinger Maestro. Comparative analysis evaluated the Glu353, His524, and Arg394 region, H12 positioning, and pocket-water dependence. WEA001 was constructed, prepared with LigPrep, and docked into prepared receptor grids using Glide Extra Precision (XP). Top-ranked poses were evaluated by GlideScore and residue-level interactions across receptor states.

Estradiol 1A52 provided the agonist benchmark, with short Glu353 and His524 contacts and a closed H12 state. Tamoxifen 3ERT showed a weakened, water-sensitive anchor network and a partially shifted H12 conformation, whereas fulvestrant-bound L536S 6SBO showed tail-driven H12 disruption. WEA001 generated favorable XP poses in L536S 6SBO (best GlideScore -7.076 kcal/mol), 3ERT (-5.341 kcal/mol), and Y537S 6CHZ (-5.092 kcal/mol). In L536S 6SBO, the WEA001 tail packed near the H12-mouth region, including Cys530, Val533, Val534, and the L536S site. No comparably stable WEA001 pose emerged in agonist-state 1A52 under the tested docking conditions.

These findings support the antagonist-design hypothesis and computationally prioritize WEA001 for evaluation in wild-type and resistance-associated ER α models, particularly L536S. This structure-guided workflow offers a testable scaffold-optimization strategy for endocrine-resistant, ER-positive breast cancer, a population with limited options after progressing on fulvestrant or CDK4/6 inhibitors. Next steps include native-ligand redocking to benchmark GlideScore, plus biochemical binding, transcriptional activity, receptor degradation, and cell-based resistance studies to define WEA001's therapeutic potential.