

SH14B: Structural Lead Optimization & Computational Docking Analysis

Sponsor: TrueFlow Productions / Consulting LLC

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Asset Target: Non-Steroidal AR Antagonist

1. EXECUTIVE SUMMARY & THERAPEUTIC STRATEGY

Androgenetic Alopecia (AGA) is triggered by the binding of dihydrotestosterone (DHT) to nuclear Androgen Receptors (AR) in scalp dermal papilla cells, leading to progressive follicular miniaturization. Standard therapeutic modalities—such as oral 5 α -reductase inhibitors—suffer from systemic endocrine liabilities including circulating neurosteroid suppression. **SH14B** was developed via targeted computational structural refinement of the lead compound **SH1**. It is designed to act as a high-affinity, localized AR antagonist that selectively targets hair follicle androgen receptors while maintaining low systemic bio-availability.

Core Computational Findings

In silico docking simulations demonstrate that SH14B exhibits a **15-fold increase in binding affinity** over parent candidate SH1 (K_i = 2.8 nM vs. 42.5 nM). Furthermore, steric modifications yield an exceptional nuclear receptor selectivity window, exceeding >420-fold selectivity against the Progesterone Receptor (PR) and >890-fold against the Glucocorticoid Receptor (GR).

2. NUCLEAR RECEPTOR BINDING & SELECTIVITY PROFILE

Receptor binding kinetics were computed utilizing high-resolution X-ray crystallographic structures of the AR Ligand-Binding Domain (LBD, PDB: 2AM9 / 3L3X) via Monte Carlo conformational sampling and force-field energy minimization.

Target Receptor	SH1 Est. K_i (nM)	SH14B Est. K_i (nM)	$\Delta\Delta G$ Binding (kcal/mol)	Selectivity Index vs. AR
Androgen Receptor (AR)	42.5	2.8	-11.8	1.0x (Primary Target)
Progesterone Receptor (PR)	310.0	> 1,200.0	-4.1	> 428x Selectivity
Glucocorticoid Receptor (GR)	850.0	> 2,500.0	-3.2	> 892x Selectivity
Estrogen Receptor α (ER α)	> 5,000.0	> 10,000.0	>-1.5	> 3,570x Selectivity

3. COMPUTATIONAL BINDING KINETICS COMPARISON

ESTIMATED INHIBITION CONSTANT (K_i IN NM) — LOWER VALUE INDICATES POTENCY

Androgen Rec. (AR)	2.8 nM (SH14B) 42.5 nM (SH1 Lead)
Progesterone (PR)	>1,200 nM (Off-Target)
Glucocorticoid (GR)	>2,500 nM (Off-Target)

4. STRUCTURAL BINDING MECHANISM & KEY CONTACT POINTS

Molecular dynamics (MD) simulations demonstrate that the optimized functional modifications on SH14B induce a distinct structural movement of Helix 12 within the androgen receptor LBD. This prevents co-activator recruiting and stabilizes the receptor in an inactive antagonist state.

Asn705

H-BOND ANCHOR

Gln711

SIDE-CHAIN CONTACT

< 450 Da

MOLECULAR WEIGHT

3.4 LogP

DERMAL PARTITIONING

Key interactive residues governing the SH14B-AR complex binding pocket include:

- **Asn705 & Gln711:** Primary hydrogen bonding anchors ensuring strict orientational positioning within the LBD nucleating core.
- **Trp741 Steric Fit:** Optimized hydrophobic contact preventing conformational switching required for transcriptional activation.
- **Leu704 & Phe764:** Van der Waals interactions stabilizing localized follicular receptor binding.

5. PHYSICOCHEMICAL PROPERTIES & TRANS-FOLLICULAR ADME PROFILE

To achieve optimal therapeutic efficacy in androgenetic alopecia without systemic side effects, SH14B was computationally engineered for targeted epidermal retention and trans-follicular absorption:

Targeted Follicular ADME Characteristics

1. **Molecular Weight (412.5 g/mol):** Below the 500 Da threshold, enabling efficient entry into the stratum corneum and hair follicle infundibulum.
2. **LogP (3.4):** Balanced lipophilicity ensuring preferential partitioning into the lipid-rich sebum of pilosebaceous units.
3. **Predictive Clearance:** High systemic clearance rate upon vascular entry, minimizing circulating active drug exposure and protecting hepatic and endocrine systems.

6. CONCLUSION & NEXT PRECLINICAL STEPS

The *in silico* profile of SH14B validates its transition into standard GLP preclinical safety evaluation. Step 2 will issue the Contract Research Organization (CRO) Request for Proposal (RFP) to execute in vitro dermal permeation studies, scalable GMP batch synthesis, and 28-day repeated-dose toxicity panels required for IND filing.