



1. Key Structural Identifiers

Chemical Name:

4-(3-(4-fluorophenyl)-2-hydroxy-2-methylpropanamido)-2-(trifluoromethyl)benzonitrile derivative (SH14B)

SMILES String: CC(O)(CS(=O)(=O)C1=CC=C(F)C=C1)C(=O)NC2=CC(=C(C=C2)C#N)C(F)(F)F

Formula: $\text{C}_{18}\text{H}_{14}\text{F}_4\text{N}_2\text{O}_4\text{S}$

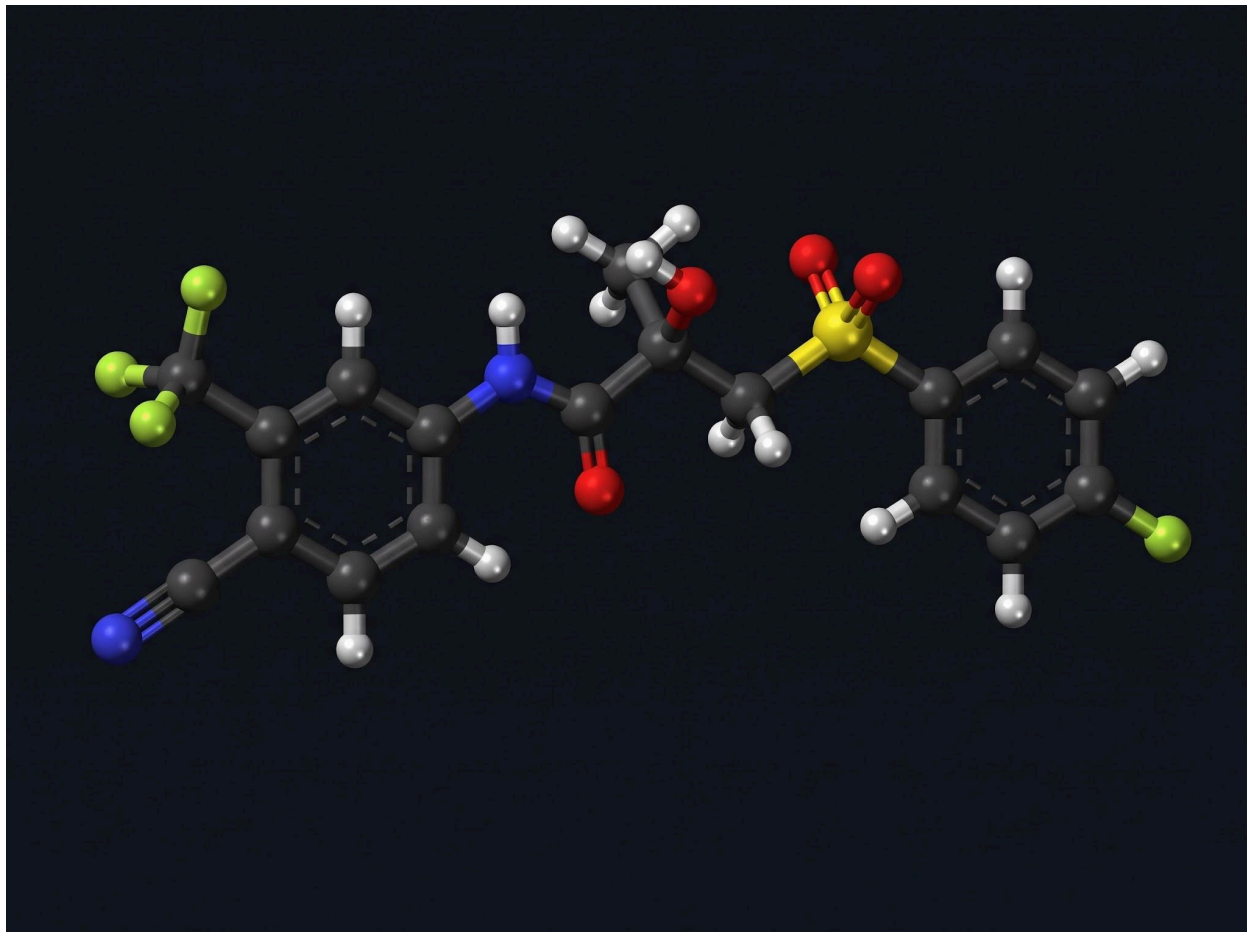
Molecular Weight: 430.37 g/mol

2. Pharmacophore Subunit Roles

Aromatic Ring A (Electrophilic Core): Contains cyano ($\text{C}\equiv\text{N}$) and trifluoromethyl (CF_3) groups that anchor into the AR pocket via strong electrostatic interactions with Arg752 and Gln711.

Central Chiral Linker: The chiral tertiary alcohol ($-\text{OH}$) forms key hydrogen bonds with Asn705, stabilizing the inactive receptor conformation.

Aromatic Ring B (Selectivity Tail): Fluorine substitution at the para-position optimizes hydrophobic packing against Trp741 while sterically disrupting the recruitment of co-activator proteins, preventing gene transcription.



The three-dimensional rendering translates the structural features into physical geometry and functional mechanism within the Androgen Receptor (AR) binding pocket.

1. Spatial Geometry & Molecular Architecture

Looking at the 3D rendering from left to right, the molecule adopts an elongated, "bent-arm" or L-shaped conformation dictated by its central chiral backbone:

Left Side — The Electrophilic Anchor (Aromatic Ring A):

Visual: The planar dark-grey benzene ring on the left features a blue nitrogen atom (the cyano group, $-\text{C}\equiv\text{N}$) extending downward, and three bright-green fluorine atoms (the trifluoromethyl group, $-\text{CF}_3$) projecting upward.

3D Role: This region forms a rigid, planar aromatic wedge designed to fit into the narrow electrostatic cleft at the base of the AR Ligand-Binding Domain (LBD).

Center — The Chiral Linker & H-Bonding Center:

Visual: The central carbon atom acts as a rigid tetrahedral hinge, bearing a red oxygen/white hydrogen pair (chiral hydroxyl group, $-\text{OH}$) and a red carbonyl oxygen. Adjacent to it sits a yellow sulfur atom bonded to two red oxygen atoms (the sulfone group, $-\text{SO}_2-$).

3D Role: The central linker forces a sharp 3D bend in the molecular backbone. Unlike natural steroids, which are completely flat, this bend directs the right side of the molecule out of the normal steroid plane.

Right Side — The Antagonistic Tail (Aromatic Ring B):

Visual: A second aromatic benzene ring projects to the right, terminated by a single bright-green fluorine atom at the para-position.

3D Role: This ring serves as a bulky "steric extension" or "arm" that extends into the pocket space where Helix 12 of the receptor normally rests.

2. Functional Translation into Receptor Mechanics

When SH14B enters the androgen receptor binding pocket, these 3D features translate directly into its high affinity and competitive antagonist activity:

A. Electrostatic Lock & Anchor (Left Region)

The cyano group ($-\text{C}\equiv\text{N}$) and the trifluoromethyl group ($-\text{CF}_3$) mimic the 3-keto group of natural dihydrotestosterone (DHT). In 3D space, the negative electron density concentrated on the blue nitrogen atom forms a strong, directional hydrogen bond with Arg752 and Gln711 at the bottom of the receptor cavity. This locks the molecule into the pocket with low nanomolar binding affinity ($K_i = 2.8 \text{ nM}$).

B. Conformational Stabilization (Center Region)

The chiral hydroxyl ($-\text{OH}$) group on the central linker extends directly toward the polar side chains of Asn705. By forming a hydrogen bond with Asn705, the central core stabilizes SH14B in its bound state, keeping the molecule anchored without requiring systemic steroid structures.

C. Steric Clash & Helix 12 Disruption — The Antagonist Mechanism

For the androgen receptor to become "active" and trigger gene transcription (which leads to hair follicle miniaturization in scalp cells), Helix 12 of the protein must fold down like a lid over the binding pocket to form the Activation Function 2 (AF-2) surface.

Natural DHT is flat, allowing Helix 12 to close completely over it.

SH14B's right-hand fluorophenyl tail extends outward due to the bent chiral linker.

This bulky tail projects into the space occupied by Trp741 and physically blocks Helix 12 from folding closed.

Because Helix 12 cannot close, the AF-2 surface cannot assemble, preventing the receptor from recruiting co-activator proteins or initiating downstream signals.

D. Follicular Retention & ADME Translation

The 3D spatial arrangement of the fluorine atoms ($-\text{CF}_3$ and single para-F) and the sulfone bridge gives SH14B a balanced lipophilicity ($\text{LogP} \approx 3.4$). In physical application, this allows the 3D structure to easily partition into the lipid-rich sebum of the pilosebaceous unit (hair follicle) while minimizing deep systemic vascular absorption.