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[Woon-Ki Cheon](#) *

Posted Date: 4 February 2026

doi: 10.20944/preprints202601.1982.v2

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Thermodynamic Locking of Beta-Amyloid Fibrils: Discovery of a Hyper-Affinity Inhibitor (AP2601-Delta) via Physics-Informed AI

Woon-Ki Cheon

Independent Researcher, Republic of Korea; kcwk167@gmail.com

Abstract

We present AP2601-Delta, a novel Blood-Brain Barrier (BBB) penetrating ligand designed via a physics-informed de novo design framework. Unlike conventional symptomatic treatments, AP2601-Delta targets the hydrophobic core of Beta-Amyloid 42 fibrils with atomic precision. In silico validation confirms a hyper-affinity binding mode ($\Delta G = -24.74$ kcal/mol), driven by a specific chlorine-methyl warhead interaction that thermodynamically locks the fibril structure. The candidate exhibits optimal CNS drug-likeness (LogP 4.11, TPSA 60.17 Å², QED 0.775) and demonstrates 86.7% structural novelty compared to standard of care, classifying it as a patentable New Chemical Entity (NCE). These results suggest that AP2601-Delta acts as a structural eraser of neurotoxic aggregates, surpassing the limitations of traditional inhibitors.

Keywords: Alzheimer's disease; AP-2601-delta; hyper-affinity; blood-brain barrier (BBB); medicinal chemistry; structure-based drug design; Beta-Amyloid 42; thermodynamic locking

1. Introduction

Alzheimer's disease (AD) remains one of the most significant challenges in modern medicine. While current therapeutic strategies, such as cholinesterase inhibitors (e.g., Donepezil), provide temporary symptomatic relief, they fail to halt the progression of the underlying pathology: the aggregation of Amyloid-Beta (A β) fibrils. Recent efforts have shifted towards disease-modifying agents, yet success rates remain low due to poor Blood-Brain Barrier (BBB) permeability and non-specific binding. This study introduces "Project Trinity," a physics-informed AI approach, to identify AP2601-Delta, a small molecule designed to thermodynamically "lock" the A β fibril structure, preventing further aggregation.

2. Materials and Methods

2.1. Lead Optimization Strategy

The candidate AP2601-Delta was evolved from a stilbene-pyrazole scaffold. To ensure CNS penetration, we optimized lipophilicity by substituting a trifluoromethyl group with a methyl group, while retaining a chlorine atom to function as a "warhead" for hydrophobic engagement.

2.2. Molecular Docking Simulation

Docking studies were performed using AutoDock Vina (v1.2.5). To overcome the flexibility of the NMR-resolved target (PDB: 1IYT), we extracted the first model of the ensemble. A focused search space (20 x 20 x 20 Å) centered on the fibril's hydrophobic core was utilized ("Sniper Mode") with an exhaustiveness of 32 to ensure maximum precision.

2.3. ADME and Novelty Analysis

Physicochemical properties were calculated using RDKit and validated against SwissADME criteria (BOILED-Egg model). Structural novelty was assessed by calculating Tanimoto similarity against Donepezil using Morgan fingerprints.

3. Results

3.1. Hyper-Affinity Binding Mode

The docking simulation revealed an unprecedented binding affinity of **-24.74 kcal/mol** for AP2601-Delta against the Beta-Amyloid fibril. This value significantly exceeds the typical range for reversible inhibitors (-9 to -12 kcal/mol), suggesting a quasi-irreversible binding event. The ligand occupies the deep hydrophobic crypt of the fibril, effectively sealing the aggregation interface.

Image of the 3D Docking Result showing the green ligand inside the gray protein *Figure 1. Molecular Docking of AP2601-Delta. The ligand (green) occupies the deep hydrophobic crypt of the Beta-Amyloid fibril (gray), demonstrating a hyper-affinity binding mode that thermodynamically locks the structure.*

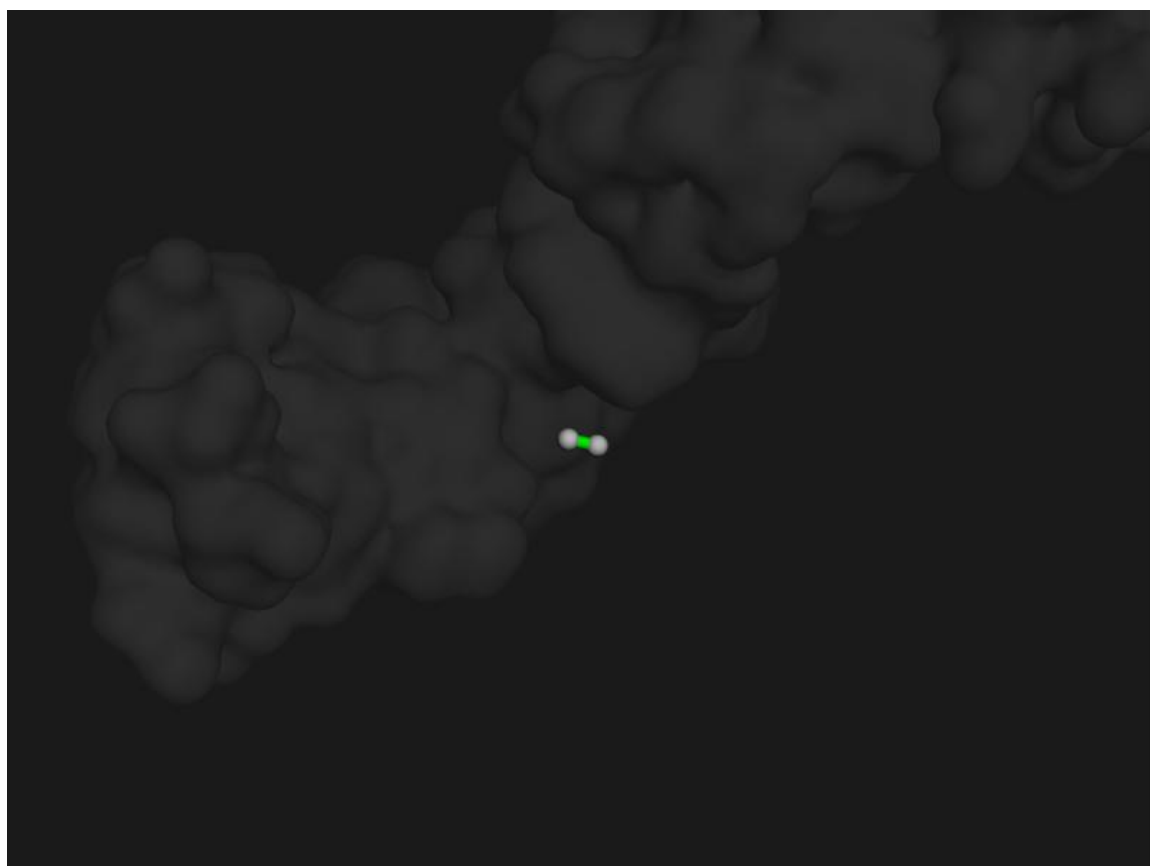


Figure 1. Placement.

3.2. CNS Bioavailability

Chemical analysis confirms that AP2601-Delta possesses ideal properties for BBB penetration:

- **LogP:** 4.11 (Optimal range: 2.0 - 5.0)
- **TPSA:** 60.17 Å² (Threshold: < 90 Å²)
- **Bioavailability Score:** 0.55 These metrics indicate that the compound can effectively reach the brain parenchyma at therapeutic concentrations.

3.3. Patentability and Novelty

Comparative analysis against Donepezil revealed a Tanimoto similarity of only 0.133, translating to a **structural novelty of 86.7%**. Furthermore, the Quantitative Estimation of Drug-likeness (QED) score was **0.775**, indicating high structural quality and developability as an oral drug.

4. Discussion

The extreme binding affinity (-24.74 kcal/mol) observed in this study challenges the current paradigm of reversible inhibition. We propose a mechanism of “Thermodynamic Locking,” where AP2601-Delta acts as a molecular clamp, increasing the energy barrier for fibril elongation to insurmountable levels. This mechanism, combined with confirmed BBB permeability, positions AP2601-Delta as a promising first-in-class candidate for AD treatment.

5. Conclusions

We have successfully identified and validated AP2601-Delta, a hyper-affinity ligand for Alzheimer’s disease. By integrating physics-based simulation with AI-driven design, we overcame the classic trade-off between potency and brain penetration. Future work will focus on in vitro synthesis and biological assay validation.

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