

Title: Cutting-edge Bioinformatics strategies for synthesizing Cyclotriazadisulfonamide (CADA) analogs in next-Generation HIV therapies

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Abstract: Cyclotriazadisulfonamide (CADA) is a macrocyclic compound known for its unique mechanism in inhibiting HIV infection by downregulating the CD4 T-cell receptor, a crucial entry point for the virus. Unlike other antiretrovirals, CADA exhibits activity against a wide range of HIV strains, as all HIV variants require CD4 binding for infection. Furthermore, CADA has shown a synergistic effect with clinically approved anti-HIV drugs, offering potential for enhanced therapeutic strategies (Vermeire & Schols, [65]). One proposed mechanism for CADA's inhibition of the CD4 receptor involves blocking the gates of the Sec61 channel, thereby preventing its translocation. However, CADA suffers from poor solubility and bioavailability. To address this, the study aimed to design CADA analogs with improved binding to the Sec61 channel, enhanced bioavailability, and reduced toxicity. The analogs were designed using SeeSAR, with Avogadro and Meeko used for 3D configuration and pseudoatom placement, respectively. AutoDock Vina version 1.2.4 was employed to predict the binding energies of these analogs. Of the 113 analogs designed, 93 demonstrated a more negative binding energy to the Sec61 channel compared to CADA. Structure-binding energy analyses were done to the top-binding analogs to show favorable structural modifications. Enzyme-ligand interactions were analyzed to elucidate the forces contributing to these binding energies. Additionally, 33 of the 113 analogs were deemed bioavailable using a bioavailability criteria specific for macrocycles. Toxicity predictions using PASS Online and StopTox identified analogs JGL023, JGL024, JGL032, and JGL047 as potential drug candidates. Molecular dynamics simulations using Gromacs-2020.4 revealed that JGL023 and JGL032 exhibited the most favorable binding to the Sec61 channel, as determined by evaluating ligand and residue flexibility, compactness, contact frequency, motion pathways, free energy, and other relevant parameters. Synthetic routes for these four analogs were proposed for future studies. The results of this study offer a new perspective on developing drugs to inhibit HIV entry.

Key words: Cyclotriazadisulfonamide (CADA) HIV inhibition CD4 receptor downregulation Sec61 channel Molecular docking Molecular dynamics simulation

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