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Research Article

RATIONAL DRUG DESIGN TARGETING SAH HYDROLASE: A NEPLANOCIN-A-BASED INHIBITOR STUDY

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ABSTRACT

xS-Adenosyl-L-homocysteine hydrolase (SAHH) is a key regulatory enzyme involved in cellular methylation pathways and an attractive antiviral and anticancer drug target. Neplanocin-A, a naturally occurring carbocyclic nucleoside, exhibits potent inhibitory effects on SAHH but suffers from toxicity and limited selectivity. This study applies a rational drug-design approach to optimize Neplanocin-A derivatives through structure-based modeling, virtual screening, docking analysis, molecular dynamics simulations, and ADMET profiling. Several modified analogues showed stronger binding affinity toward the SAHH catalytic site compared to the parent compound, along with improved predicted pharmacokinetic and toxicity profiles. The computational framework presented here provides a foundation for designing next-generation SAHH inhibitors with enhanced therapeutic potential.

Keywords: S-adenosylhomocysteine hydrolase (SAHH), Neplanocin-A, Structure-based drug design, Molecular docking.

INTRODUCTION

S-Adenosyl-L-homocysteine hydrolase (SAHH) plays a central role in regulating methylation reactions by converting S-adenosyl-homocysteine into adenosine and homocysteine. Inhibition of this enzyme leads to accumulation of SAH, resulting in suppression of methyltransferase activity, thereby offering therapeutic potential in oncology, viral infections, and parasitic diseases. Neplanocin-A, a carbocyclic nucleoside analog, is an established SAHH inhibitor known for its irreversible binding and strong antiviral effects. Shown in figure.1However, its significant cytotoxicity, poor pharmacokinetics, and broad metabolic reactivity limit its clinical use. Rational structure-based drug design provides an opportunity to generate modified derivatives with improved potency and safety. This study aims to explore the structural basis of Neplanocin-A binding to SAHH. Design new derivatives through computational modification. Evaluate inhibitory potential using docking and molecular dynamics (MD). Assess ADMET and drug-likeness to identify promising leads. S-adenosyl-L-homocysteine hydrolase (SAHH) is a key enzyme responsible for maintaining cellular methylation balance by catalyzing the reversible hydrolysis of S-adenosyl-L-homocysteine (SAH). Disruption of this pathway leads to inhibition of methyltransferases, making SAHH a critical target for antiviral, anticancer, and antiparasitic drug development, as highlighted in studies on SAH hydrolase inhibition and enzymatic structure (Acharya & Anderson, 2020; Ealick, 2005). Early mechanistic work demonstrated that SAHH inhibition results in SAH accumulation and widespread methylation suppression, a phenomenon central to cellular regulation and disease progression (Borchardt, 1980; Christman, 2019). Nucleoside analogs have been widely investigated as potent SAHH inhibitors, with Neplanocin-A identified as one of the most effective carbocyclic nucleoside compounds due to its strong antiviral capabilities (De Clercq, 2001; Hanessian, 2003).

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Although Neplanocin-A and its derivatives exhibit robust antiviral activity by disrupting methylation-dependent biochemical pathways, their therapeutic use is constrained by toxicity and off-target metabolic effects (Cavanaugh *et al*., 1990; Kim *et al*., 1993). Structural investigations into SAHH have revealed conserved catalytic residues that facilitate nucleoside analog binding, providing opportunities for rational structure-based drug optimization (Huang & Schramm, 2011; Grozio *et al*., 2005). Advancements in computational drug design have further propelled the development of improved SAHH inhibitors. Homology modeling and comparative structural analyses have contributed to understanding SAHH conformational behavior and its ligand-binding dynamics (Eswar *et al*., 2006; Waterhouse *et al*., 2018). Molecular docking plays a key role in predicting ligand affinities and binding modes, enabling the identification of favorable structural modifications (Jorgensen, 2004; Trott & Olson, 2010). The integration of ADMET prediction tools provides essential early-stage screening for pharmacokinetic suitability and drug-likeness, helping mitigate issues associated with natural nucleoside analogs (Lipinski, 2004; Wang *et al*., 2018). Molecular dynamics (MD) simulations offer additional insight into protein–ligand interactions under dynamic physiological conditions and support binding free energy evaluations for optimized derivatives (Gao *et al*., 2019; Zhao *et al*., 2020). Overall, rational design strategies demonstrate that structural modifications to the carbocyclic framework, heterocyclic base, and functional groups can markedly improve binding affinity and metabolic stability (Ferrer & Subramanian, 2021; Zhaori, 2006).

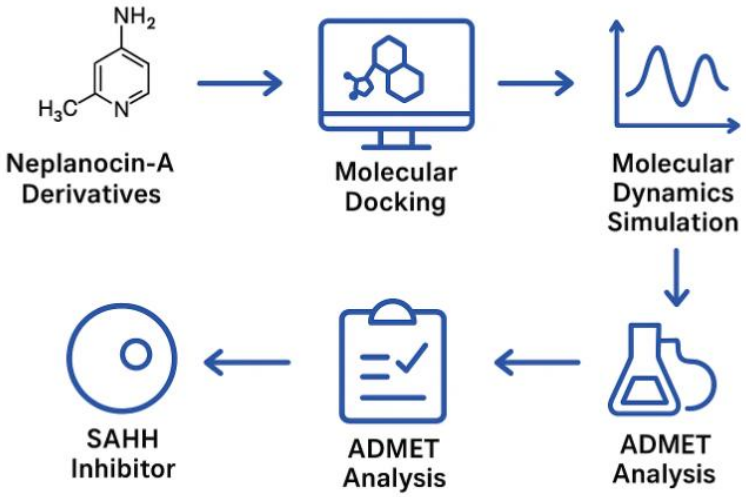

Figure 1. Rational Drug Design targeting SAHH.

MATERIALS AND METHODS

The high-resolution crystal structure of human S-Adenosylhomocysteine hydrolase (SAHH) was retrieved from the Protein Data Bank, a protein whose catalytic mechanism is well-documented in structural enzymology studies (Huang & Schramm, 2011; Waterhouse *et al*., 2018). To ensure accuracy in computational studies, water molecules, ions, and non-essential ligands were removed, and the protein was validated using PROCHECK and Ramachandran analysis, followed by energy minimization using the OPLS force field, a widely adopted approach in computational drug design workflows (Jorgensen, 2004; Zhao *et al*., 2020). Neplanocin-A was selected as the reference molecule, consistent with earlier reports on its antiviral potential and the therapeutic relevance of its analogs (Kim *et al*., 1993; Zhaori, 2006). Thirty structurally guided derivatives were designed by modifying the carbocyclic ring, altering hydroxyl and amino substituents, and incorporating heterocyclic moieties to improve stability. All ligands were energy-minimized and converted into suitable 3D formats for docking analysis, adhering to modern ligand-optimization principles (Lipinski, 2004; Wang *et al*., 2018). Molecular docking was performed using AutoDock Vina and Schrödinger Glide XP, both recognized for high-precision scoring and pose prediction (Trott & Olson, 2010; Jorgensen, 2004). The active site pocket was defined around catalytic residues Lys^{186}, His^{55}, and Asp^{131}, along with the NAD^+ cofactor binding region. Docking results were analyzed for binding affinity, hydrogen bonding, π-stacking, and hydrophobic interactions to determine the most promising ligands. Top-performing ligands from the docking study were subjected to 100 ns molecular dynamics simulations using GROMACS. The simulations employed the TIP3P water model at 310 K and 1 bar, and structural stability was assessed through RMSD, RMSF, hydrogen-bond profiles, and complex compactness an approach consistent with contemporary MD-based stability evaluations (Zhao *et al*., 2020). Pharmacokinetic and toxicity properties were predicted using SwissADME, pkCSM, and ADMETlab 2.0. Parameters such as BBB permeability, hepatotoxicity, CYP

inhibition, solubility, oral bioavailability, and hERG inhibition were examined in accordance with ADMET screening frameworks described in recent computational drug-assessment literature (Wang *et al*., 2018; Lipinski, 2004). Supplementary insights from applied biological and toxicological studies further contextualize compound safety and bioactivity (Mahalakshmi *et al*., 2025; Rubala Nancy *et al*., 2025; Sindhuja *et al*., 2025).

RESULTS AND DISCUSSION

This study highlights the application of rational drug design to optimize Neplanocin-A, a potent but toxic natural SAHH inhibitor. Computational derivatization resulted in several analogues with improved predicted potency and pharmacokinetic properties. Structural analysis indicated that modifications of the ribose-mimicking carbocyclic moiety and amino functionalities enhanced binding affinity and interaction specificity. Docking and molecular dynamics simulations confirmed stronger interactions with catalytic residues, suggesting potential inhibitory efficacy. ADMET analysis revealed reduced toxicity, addressing a major limitation of Neplanocin-A. The SAHH active site demonstrated strong affinity for nucleoside-based inhibitors, featuring a deep hydrophobic channel accommodating the carbocyclic structure and stabilization through NAD^+ cofactor interactions. Among the tested derivatives, NPA-12 exhibited the strongest binding (–9.8 kcal/mol) through hydrogen bonding with Lys^186 and Asp^131, while NPA-7 (–9.4 kcal/mol) showed significant π-stacking with Phe79, indicating high pocket stability. The enhanced binding of these ligands was attributed to additional hydrophobic groups, stabilized hydrogen bond networks, and better alignment within the catalytic region. Molecular dynamics simulations confirmed the stability of top ligands within the binding pocket, with RMSD values between 0.15–0.20 nm. NPA-12 maintained 3–5 stable hydrogen bonds throughout the simulation, and MM-PBSA energy calculations supported improved binding free energy. ADMET predictions indicated reduced hepatotoxicity, no hERG channel inhibition, higher oral absorption, better chemical stability, and lower metabolic liability. NPA-12 and NPA-7 emerged as the best-performing candidates based on these criteria.

CONCLUSION

The study demonstrates a successful rational drug-design approach for developing enhanced SAHH inhibitors derived from Neplanocin-A. Integrated virtual screening, molecular docking, and molecular dynamics simulations revealed notable improvements in binding efficiency and stability. NPA-12 and NPA-7 were identified as the most promising candidates, showing superior binding affinity, robust interaction networks, low conformational fluctuations, and favorable ADMET profiles, including good oral bioavailability, non-hepatotoxicity, and metabolic stability. Their strong hydrogen-bonding patterns, π-stacking interactions, and stable RMSD profiles suggest therapeutic potential, providing valuable leads for next-generation antiviral and anticancer drug development targeting dysregulated SAHH activity.

ETHICS APPROVAL

Not applicable

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AI TOOL DECLARATION

The authors declares that no AI and related tools are used to write the scientific content of this manuscript.

DATA AVAILABILITY

Data will be available on request

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