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Discovery and Molecular Docking of an SLC29A1 Inhibitor

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Abstract. The equilibrative nucleoside transporter 1 (ENT1/SLC29A1) plays a critical role in cellular nucleoside homeostasis and has emerged as a promising therapeutic target for cancer, cardiovascular diseases, and metabolic disorders. This study employed molecular docking techniques to identify and characterize novel SLC29A1 inhibitors using the high-resolution crystal structure of hENT1 (PDB ID: 6OB6). Four candidate compounds (C27-F, C27-E9, C27-E9.1, and C27-E9.2) were evaluated for their binding interactions, revealing strong affinities to key residues (Gly154, Trp29) and transmembrane domains (TM1, TM7, TM9) involved in nucleoside transport. Among these, C27-E9.2 exhibited the highest docking score, suggesting superior inhibitory potential by mimicking the steric occlusion mechanism of established inhibitors like dilazep and NBMPR. The findings highlight the therapeutic promise of these compounds in modulating hENT1 activity, particularly in overcoming gemcitabine resistance in pancreatic cancer and enhancing adenosine-mediated cardioprotection. However, further experimental validation is required to confirm their efficacy and pharmacokinetic suitability. This study not only advances the development of targeted hENT1 inhibitors but also contributes to the broader understanding of solute carrier (SLC) transporters as druggable targets, paving the way for precision medicine applications in oncology and beyond.

Keywords: SLC29A1, hENT1, nucleoside transporter, molecular docking, inhibitor discovery

1. Introduction

As important precursors of nuceotides and nucleic acid, nucleosides drive the force of obligate transportation system to pass through the kinetic barrier of the lipid bilayer system, functioning in human metabolism, physiology and pharmacology. By regulating the concentration of purine and pyrimidine nucleosides around cell membrane, nucleoside transporters (NT) are classified into two major categories, including equilibrative nucleoside transporters (ENT) depending on concentration gradient and concentrative nucleoside transporters (CNT) coupling with sodium transport. As human CNT encoded by gene family SLC28 is mainly found in intestinal and renal epithelial cells as well as other specialized cell types, while homo species ENT encoded by SLC29 is generally present in almost all cell types. In mammalian cells, CNT is regulated by nutrients in intestinal epithelial cells, however, when cells are exposed to proliferation stimuli, the quantity of ENT proteins (mainly

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ENT1) increases, indicating that NT can also play a compensatory physiological role despite of regulating adenosine concentrations.

Representing the biggest family of transporters (>400members) throughout the membranes of organelles and the plasma membrane, the SLC superfamily provide the therapeutic opportunities for small molecules as modulators due to the well investigated atomic resolution structures and alternating exposure transport mechanism [1,2]. Most SLC proteins (~83%) tend to contain 7 to 12 TM domains and have a verified unique feature of the pseudo-symmetry of cross-core transmembrane (TM) domains [2]. While SLC28 proteins represent a higher affinity for substrates than SLC29 proteins, SLC29 proteins have a higher turnover number in transportation, which offer prospects for substrate analog to bind SLC29 that facilitate further targeted therapeutic approaches. Moreover, among the four subtypes of ENT, ENT1 (SLC29A1) is most well-studied.

As human ENT1 (hENT1) is the first sodium-independent nucleotide transporter to be cloned, it has a strong inhibitory effect on NBMPR with half-maximal inhibitory concentration (IC50) up to the range of sub-nanomolar to low nanomolar [3]. With 456 amino acid residues to comprise 11 transmembrane helical segments that are mostly connected by short hydrophilic regions, the amino terminus of ENT1 is located inside the cell while the carboxyl terminus is located outside [4]. Otherwise, the large glycosylated extracellular loop between TM1 and TM2 as well as the central cytoplasmic loop between TM6 and TM7 seem to be unaffected to general functional properties of transport and inhibition [4,5]. As for the crystal structure, the first available experimental structure of ENT family member is the engineered functional variant of crystallizable hENT1, which is biochemically stable [6]. As SLC proteins represent two most common structural folds of the major promoter superfamily (MFS) consisting of two pseudo-duplications of six TM helices connected by the cytoplasmic ring and leucine transporter (LeuT) -like folds composed of two 5-TM containing bundle and scaffold domains, ENT1 is generally categorized as MFS-like structures [7]. However, it turns out to be some obvious differences when superimpose the structures of hENT1 with various MFS transporter structures to evident the homology [6]. There is a lack of the canonical TM12 lead to slight displacement of TM9 in ENT1, which results in a pseudosymmetry, compared to the level of internal 2-fold symmetry apparent in MFS [6]. It is speculated that the lower internal 2-fold symmetry provides a gating mechanism of rocker switch that is divergent from that of MFS [8]. (Figure 1) It has been demonstrated that the conformational transition of HENT1 from the open state to the metastable closed state is mainly driven by TM1, TM2, TM7 and TM9 through the method of comparative long-time unbiased molecular dynamics simulations [9]. Therefore, owing to the absence of an extra essential C-helix transporter (TMs 3, 6 or 12) during evolution in the structure of hENT1, it reveals the availability of achieving function of transporters without adhering to the strict 12-TM topological structure of MFS [8]. In order to enhance the transport cycle during the transformation process of hENT1, the conformational changes of three hENT1 systems namely hENT1_apo (ligand free), hENT1_adenosine (B, C, D), and hENT1_dilazep are analyzed through comparative long-time unbiased molecular dynamics (MD) simulations [6,9]. The concrete structure of dynamic ENT1 can mainly include three parts, among which the central cavity is of great significance for substrate recognition, transportation and inhibitor binding. Located at the center of ENT1, the center cavity enclosed by thick gate and thin gate is highly hydrophilic, preventing the solvent of the external solution from entering [8]. Positioning inside ENT1, the thick gate forms a highly hydrophobic network of large volumes that blocks the release of nucleotides from the central cavity [8]. Meanwhile, the thin gate consists of TM1 and TM7 allows the solvent to enter the external solution from the central cavity but prevents the release of nucleotides [8]. The transitions of gate formation and destruction state allow solutes to alternately enter the central cavity located

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between two symmetrical transporters for further transportation. When Dilazep bind to hENT1, the inhibitory may be achieved by steric hindrance of extracellular thin gate occlusion, completely sealing the central cavity from the extracellular solution through the rearrangement of TM1 and TM7 [6,8]. However, the restrain occurs by occupying the site close to the substrate binding cavity when NBMPR binds while hENT1 transporter adopts a conformation similar to that of the dilazep binding structure [6,10]. Meanwhile, similar to NBMPR, ethanol occupies the distal end of the cavity to achieve inhibition while the I216T mutation on TM6 of hENT1 can lead to a change in the binding affinity of ethanol at this site [11]. This polymorphism is related to slc29a1 and is associated with alcohol dependence with withdrawal seizures.

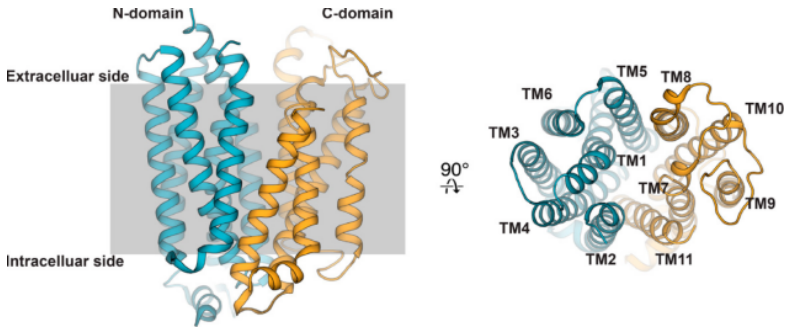

Figure 1. The structure of hENT1-dilazep

The diagram offers a detailed depiction of the high-resolution crystal structure of the hENT1-dilazep cocrystal structure (PDB 6OB7). The initial six transmembrane helices are represented by the color blue (N-domain) while the subsequent five transmembrane helices are designated by the color orange (C-domain) [8].

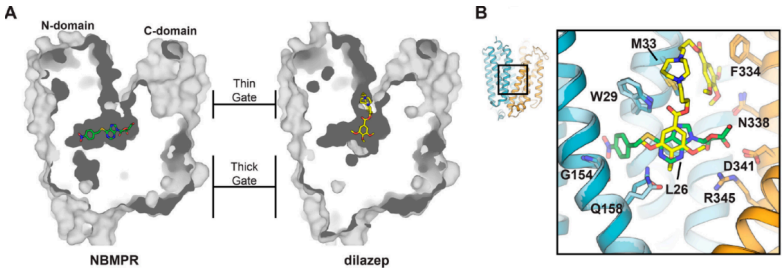

Figure 2. The structure of hENT1 binding with its ligands

The figure depicts NBMPR and dilazep binding sites in human ENT1, with NBMPR illustrated in green and dilazep in yellow (PDBs 6OB6 and 6OB7, respectively). The subsequent section provides a detailed presentation of inhibitor-transporter interactions. The domain's protein composition has been delineated with the employment of colour coding. Specifically, the domain's N-terminal segment has been designated blue, whilst the C-terminal segment is designated orange (with lighter shades of either colour employed for the NBMPR human ENT1 cocrystal structure). The residues involved in interaction are illustrated by means of sticks [8].

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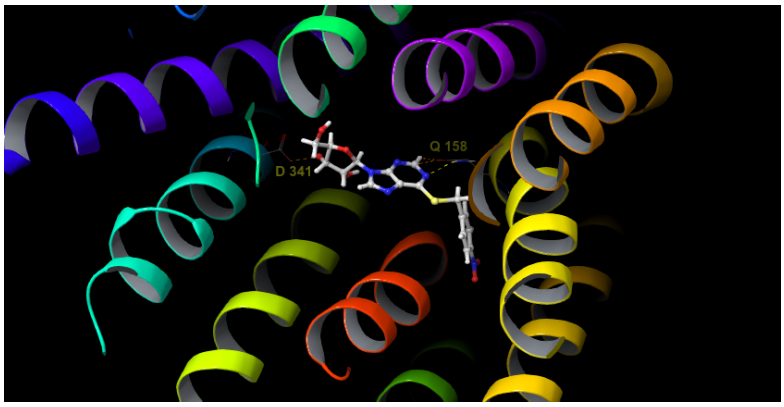

Figure 3. The picture demonstrates the interaction of ENT1 (helix) and NBMPR (ball and stick structure) using Schrodinger

It has been examined that the binding kinetics of ENT1 inhibitors, with the objective of identifying improved inhibitors for the treatment of heart disease, stroke, and cancer.

As hENT1 is closely related to diseases, abundant nucleoside drugs are designed for binding to hENT1 that function as either permeant or inhibitors. Whenever ENT1 is overexpressed, molecules that reduce the activity of ENT1 are proposed as an additional treatment for cancer, ischemic heart disease, infarcts, stroke and inflammatory diseases. As apoptotic brown adipocytes enhance energy expenditure via extracellular inosine, knocking down ENT1-mediated inosine reuptake could promote the differentiation of brown adipocytes, thereby promoting cardiometabolic health [12]. Aiming at developing novel vasodilators, the flow cytometry assessment was used to identify highly potent dipyridamole analogues as inhibitors of ENT1. In cases of cardiac effects such as ischemia and hypertension, directly inhibiting ENT1 to increase extracellular adenosine levels can lead to the development of adenosine reuptake inhibitors such as draflazine, as well as the commercially available antithrombotic drugs dipyridamole and dilazep. Generally, despite the binding of inhibitors, SLC29a1 can also treat diseases by transporting drugs, such as the widely known drugs including gemcitabine against viral infections and ribavirin employed in some types of cancer. In the pursuit of novel hENT1 inhibitors, the affinity of 39 ST7092 derivatives was assessed, thereby underscoring their potential as covalent molecular tools [13].

Significant advancements have been achieved in the research of hENT1-related therapeutic strategies in recent years. It was demonstrated before that BCR-ABL tyrosine kinase inhibitors (TKIs) could selectively inhibit hENT1, thereby modulating the uptake of anticancer drugs, with Nilotinib exhibiting the strongest inhibitory effect on hENT1. Additionally, a gemcitabine prodrug named WRQ-2 exhibited high toxicity and effectively reversed drug resistance induced by hENT1 inhibition. In 2023, SAENTA-Cy5 probe and dSTORM technology were employed to elucidate the assembly pattern of hENT1 on the membrane, offering novel insights into its biological function [14]. Moreover, by targeting Slc29a1, miR-33-3p inhibits PC12 cell proliferation and promotes neuro-like differentiation [15]. Although this study did not directly involve hENT1, its results highlight the broad role of nucleoside transporters in cell proliferation and differentiation.

It was found in 2016 that the polymorphism of the SLC29A1 transporter (ENT1) was associated with complete remission outcomes in AML, underscoring its importance in AML treatment [16]. In 2018, research explored the expression of drug-metabolized enzyme genes in the treatment response of AML through real-time PCR technology, wihch provides important gene expression data support for understanding the predictive and prognostic role of hENT1 in chemotherapy [17]. Furthermore, the expression of transport proteins hENT1 was observed by analyzing nucleosides in pediatric

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acute myeloid leukemia samples, which indicates the expression levels of these proteins are not significantly related to the survival rate of patients or drug sensitivity, further reveals the complex regulatory mechanism of hENT1 in acute myeloid leukemia and its potential clinical implications [18].

A substantial body of research has demonstrated a close correlation between the expression level of hENT1 and patients' response to gemcitabine treatment in the context of pancreatic cancer. A correlation between hENT1 expression and gemcitabine response in cholangiocarcinoma (BTC) cell lines and patients was identified in 2018, thereby substantiating the prospective application of hENT1 as a predictive biomarker [19]. In the context of gemcitabine resistance, a 2020 study revealed that modulating hENT1 levels in pancreatic cancer cells could reverse resistance primarily by altering glycolysis and glucose transport mechanisms [20]. A 2021 study indicated that low CDA mRNA levels combined with hENT1 expression could predict the superiority of gemcitabine over 5-FU, suggesting promising applications for hENT1 in combination therapies [21]. A 2022 study examined the relationship between hENT1 expression and chemotherapy response, revealing that hENT1 mRNA expression can serve as a predictive biomarker for the response of advanced pancreatic ductal adenocarcinoma patients to gemcitabine and Nab-paclitaxel [22].

From a clinical perspective, a study suggested that hENT1 and RRM1 markers enhance gemcitabine efficacy in pancreatic cancer, although further clinical trials are necessary for validation [23]. This finding was confirmed in 2023, which demonstrated that high hENT1 expression correlates with increased survival rates in resectable pancreatic cancer patients receiving gemcitabine-based adjuvant intra-arterial chemotherapy [24]. In 2019, a multimodal evaluation revealed that the hENT1 antibody 10D7G2 and mRNA could effectively predict the benefits of gemcitabine in patients with pancreatic ductal adenocarcinoma (PDAC) [25]. A 2024 study investigated the prognostic and predictive functions of hENT1 in advanced pancreatic ductal adenocarcinoma (PDAC), revealing that a high combined score is associated with enhanced disease control rate (DCR) and progression-free survival (PFS) [26]. Collectively, these findings underscore the potential of hENT1 in predicting chemotherapy responses and evaluating overall prognosis in pancreatic cancer.

While the majority of studies have focused on NSCLC, analogous findings have been observed in other cancer types. For instance, a study conducted before observed that G6PD deficiency influences hENT1 expression in β-thalassemia patients, thereby potentially resulting in pathological alterations. This mechanism may be applicable across different types of cancer and warrants further investigation. In the 2016 study, the expression levels of hENT1 were compared in non-Hodgkin's lymphoma cell lines, and variability in their expression patterns was identified, providing novel insights for precision medicine [27]. While the present study focused primarily on non-Hodgkin's lymphoma, its findings are relevant to understanding the role of hENT1 in other cancer types. Additionally, hENT1 was detected by comparing antibodies in extrahepatic cholangiocarcinoma (ECC), revealing that the 10D7G2 antibody has prognostic significance [28]. Regarding gastric cancer, a study in 2021 showed that hENT1 pathway was targeted to inhibit the proliferation of gastric cancer MGC803 cells and promote apoptosis by miR-26b [29]. In conclusion, the mechanisms and clinical significance of hENT1 in various cancers and other diseases are gradually being elucidated, offering new perspectives and potential targets for future diagnosis and treatment.

Significant advancements have been made in researching hENT1 as a predictive marker in cancer chemotherapy. By up-regulating hENT1 and miR-143, the resistance of triple-negative breast cancer (TNBC) to gemcitabine could be reversed, which provides a new idea for overcoming chemotherapy resistance [30]. Also, the role of hENT1 in the gemcitabine sensitivity of high-grade meningiomas

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was explored [31]. These studies jointly demonstrate that hENT1 has significant predictive value in the chemotherapy response and prognosis of various cancer types. These studies jointly emphasize the crucial role of SLC29A1 in the prognosis of HCC patients and suggest its potential in cancer treatment.

Additionally, ENT1 plays a dominant role in placental transfer of the antiretroviral drug abacavir, helping to prevent mother-to-child HIV transmission [24]. These findings suggest that hENT1 not only has an important role in cancer chemotherapy, but may also play a key role in the diagnosis and treatment of other diseases.

By the reason of foregoing, it is of necessity to discover more moleculars act as inhibitors for future drug development due to the significance of the SLC29A1 target.

2. Method

The structure of protein Slc29a1 (PDB ID: 6OB6) from RCSB database (https://www.rcsb.org/) is treated in Maestro11.9 platform for processing. Protein preparation Wizard was used at the beginning to add hydrogen atoms, optimize hydrogen bond networks and protonation states, process missing atoms and residues as well as crystalline water molecules and cofactors, form disulfide bonds, eliminate steric conflicts, and minimize constrained energy for standardizing chemical accuracy, structural integrity and plausibility.

The structures of the docking compounds (C27-F, C27-E9, C27-E9.1, C27-E9.2) were drew in ChemDraw and imported into Chem3D software using the MM2 module for optimization and energy minimization. After that, the ligands were saved as sdf files and prepared in Maestro11.9 through Ligprep module for 3D structure generation and optimization, exploring protonation state (ionization state), tautomer, stereoisomer and ring conformation as well as normalizing and correcting structure.

At the beginning, the Receptor Grid Generation preprocessing procedure was performed to define the central coordinates and spatial range of the protein binding pocket based on the known ligand (NBMPR) positions. (Figure 3) This process established a 3D grid space, which effectively narrowed the search area for subsequent ligand docking. Meanwhile, receptor chemistry was mapped, receptor structural flexibility was processed, metal ion interactions in active sites were identified, and water molecules were added. After that, molecular docking of the prepared protein and four ligands was completed by ligand docking and induced fit docking modules in Schrodinger Maestro software through standardized docking methods.

The interaction mode between the compounds and the target protein was analyzed to identify specific interactions with protein residues, such as hydrogen bonding, π–π stacking, hydrophobic interactions and the stability of energy. Subsequently, the docking score of the compound was evaluated to infer whether the screened compound may exhibit a potential biological activity.

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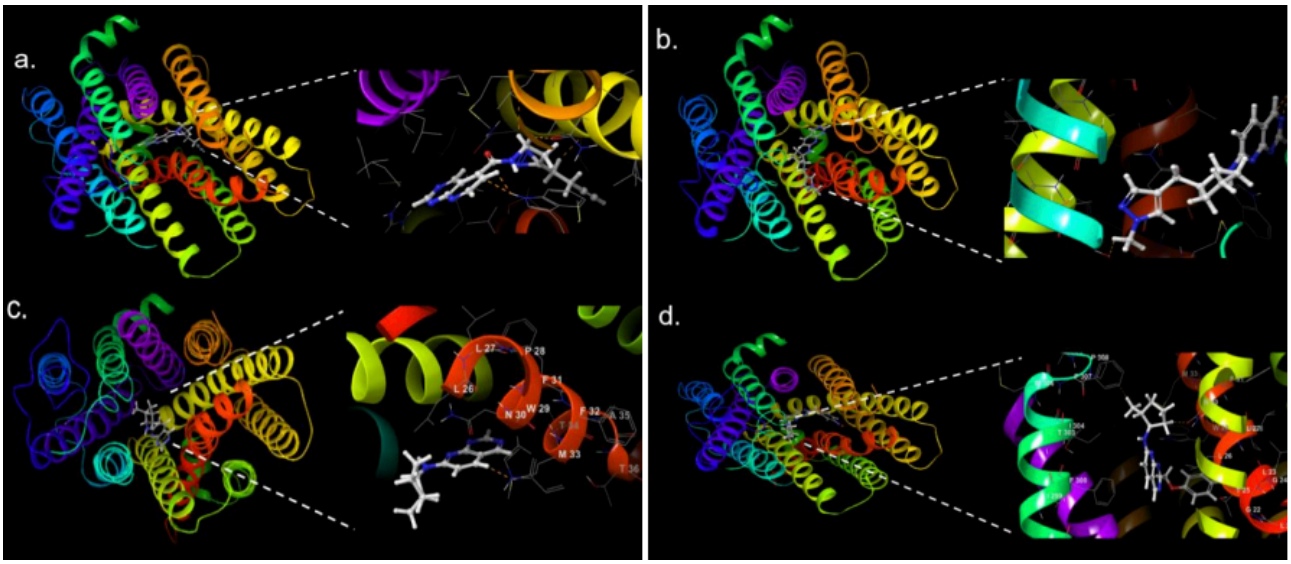

Figure 4. The diagrams show the ligand docking results using XP resolution after being merged, which represents the interaction between protein slc29a1 and C27-F, C27-E9, C27-E9.1, C27-E9.2 separately

3. Discussion

The discovery and molecular docking of novel SLC29A1 (hENT1) inhibitors represent a significant advancement in targeting nucleoside transporters for therapeutic applications. The study leveraged computational approaches to evaluate the binding interactions of four candidate compounds (C27-F, C27-E9, C27-E9.1, and C27-E9.2) with hENT1, revealing critical structural and functional insights. The docking results demonstrated that these compounds exhibit strong binding affinities, primarily through interactions with key residues such as Gly154, Trp29, and transmembrane helices (TM1, TM7, and TM9), which are known to play pivotal roles in hENT1's transport mechanism. These findings align with previous studies on established inhibitors like dilazep and NBMPR, which also target the central cavity of hENT1, obstructing nucleoside translocation via steric hindrance. The high docking scores of C27-E9.2 suggest its superior inhibitory potential, positioning it as a promising lead compound for further optimization. Importantly, the study highlights the structural flexibility of hENT1, particularly in its extracellular thin gate (TM1 and TM7), which undergoes conformational changes during substrate transport—a feature that these inhibitors exploit to achieve their blocking effect. (Figure 4)

The therapeutic implications of these findings are profound, particularly in oncology and cardiovascular medicine. hENT1 is a well-documented biomarker for gemcitabine sensitivity in pancreatic cancer, where its overexpression correlates with improved patient survival. By inhibiting hENT1, these compounds could potentially modulate intracellular nucleoside levels, either enhancing the efficacy of nucleoside-based chemotherapies or reversing drug resistance in malignancies. Additionally, hENT1's role in adenosine reuptake makes it a compelling target for cardiovascular diseases, where increased extracellular adenosine can promote vasodilation and cardioprotection. The study's computational results provide a foundation for developing dual-purpose inhibitors that could benefit both cancer and ischemic heart disease treatments. However, while the docking data are promising, translational challenges remain, including the need for experimental validation through in vitro transport assays and in vivo efficacy studies. Furthermore,

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pharmacokinetic properties such as solubility, metabolic stability, and bioavailability must be optimized to ensure clinical applicability.

Table 1. The table below demonstrates the ligand docking statistics by both XP and SP while the appendix are also depicted. It can be witnessed obviously that C27-E9 owns the best docking score of -7.649, however, C27-E9.2 displays the highest absolute docking value of -7.932

Docking Molecules	Ligand Docking score (XP)	Ligand Docking score (SP)
C27-F	-5.543	-4.001
C27-E9	-7.649	-7.316
C27-E9.1	-6.189	-6.517
C27-E9.2	-6.990	-7.932

Beyond immediate therapeutic applications, this research contributes to a broader understanding of solute carrier (SLC) transporters, a protein superfamily with immense pharmacological potential. The structural insights gained from hENT1 inhibition could inform the design of modulators for other SLC transporters, expanding the scope of targeted drug development. Future studies should explore the dynamic behavior of hENT1-inhibitor complexes using advanced techniques like molecular dynamics simulations to refine binding models. Additionally, structure-activity relationship (SAR) studies could guide the synthesis of derivatives with enhanced potency and selectivity. Collaborative efforts between computational and experimental researchers will be essential to bridge the gap between virtual screening and real-world drug candidates. Ultimately, this work underscores the importance of hENT1 as a druggable target and paves the way for innovative treatments in precision medicine.

4. Conclusion

In summary, this study successfully identified and characterized novel SLC29A1 inhibitors through molecular docking, demonstrating their potential to modulate nucleoside transport with implications for cancer therapy and cardiovascular disease management. The computational analysis revealed that the candidate compounds, particularly C27-E9.2, exhibit strong binding interactions with hENT1, mimicking the inhibitory mechanisms of known blockers like dilazep and NBMPR. These findings not only validate hENT1 as a viable therapeutic target but also provide a structural blueprint for designing next-generation inhibitors. The research aligns with clinical observations linking hENT1 expression to drug response, reinforcing its relevance in personalized medicine. However, the transition from in silico predictions to clinical applications requires rigorous experimental validation, including biochemical assays and preclinical testing, to confirm efficacy and safety.

The broader significance of this work lies in its contribution to the growing field of SLC transporter pharmacology. By elucidating the binding dynamics of hENT1 inhibitors, the study offers a framework for exploring other SLC family members, many of which remain underexploited in drug development. Future directions should focus on optimizing lead compounds for improved pharmacokinetics and conducting mechanistic studies to unravel the full therapeutic potential of hENT1 modulation. Collaborative interdisciplinary research will be key to advancing these discoveries from bench to bedside.

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Ultimately, this study highlights the power of computational drug discovery in identifying novel inhibitors for challenging targets like hENT1. As precision medicine continues to evolve, the ability to selectively modulate nucleoside transporters will open new avenues for treating resistant cancers, metabolic disorders, and cardiovascular conditions. The findings presented here mark a critical step toward that goal, offering hope for more effective and tailored therapies in the years to come.

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