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Design, synthesis, and molecular docking of novel urea linked 1,2,3-triazole-benzenesulfonamide hybrid as potential carbonic anhydrase inhibitors

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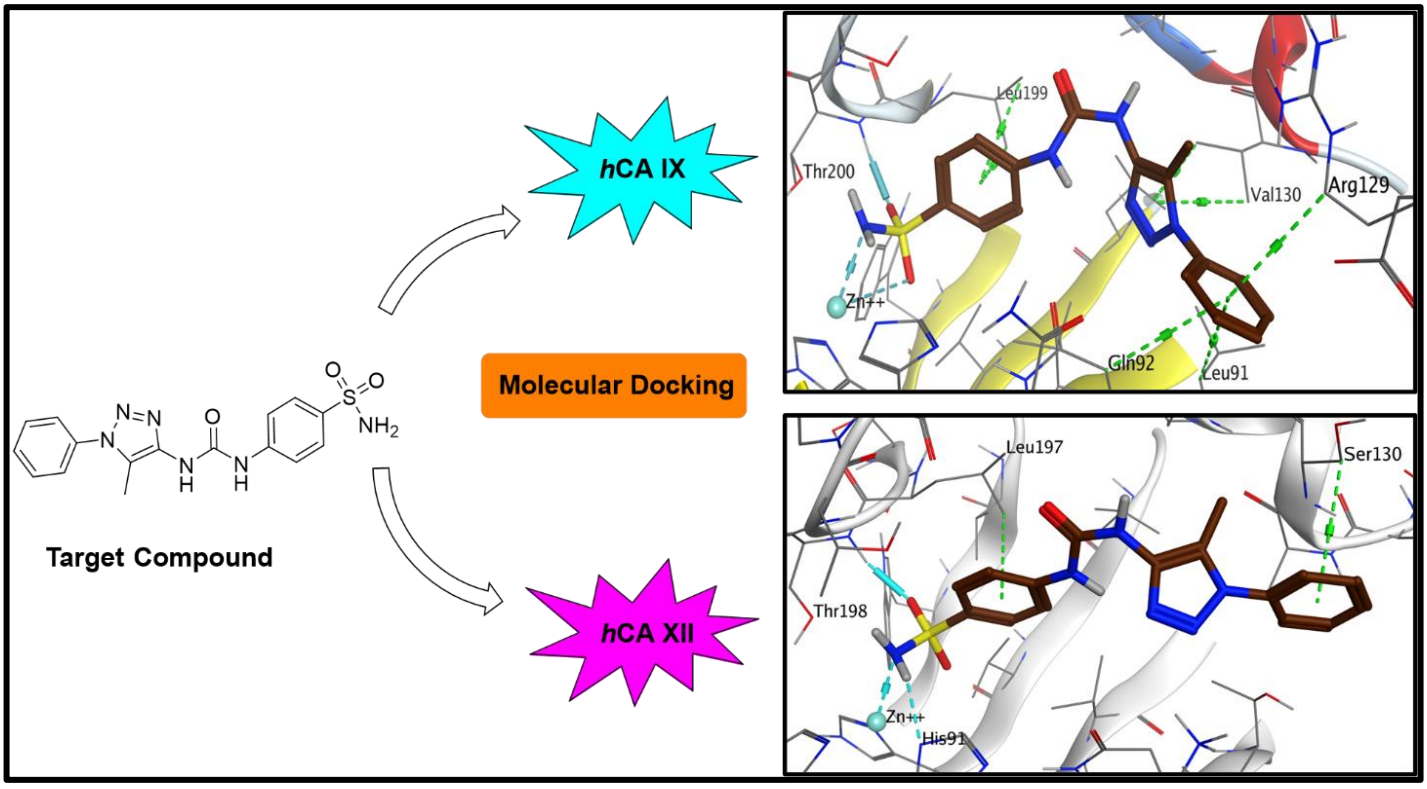
Abstract

Solid tumors often exhibit hypoxia, a condition resulting from rapid tumor growth that outpaces oxygen supply. This hypoxic environment promotes angiogenesis and enhances tumor survival while reducing the effectiveness of anticancer drugs. SLC-0111, a specific inhibitor of human carbonic anhydrase (*h*CA) IX, is currently being investigated in clinical trials as a potential therapeutic option for hypoxic malignancies. In this study, we describe the synthesis of a novel compound analogue to SLC-0111 by replacing the para-fluorophenyl tail with a phenyl triazole motif. Our aim is to investigate the potential of this new compound as an inhibitor of the cancer-associated *h*CA IX and *h*CA XII isoforms. Molecular docking was performed on compound **6** to elucidate its possible binding interactions within the active sites of target enzymes. The hybrid compound exhibited strong binding affinity towards *h*CA IX and *h*CA XII isoforms, with higher binding free energy (DG) values (-6.9682 to -5.5453 Kcal/mole) compared to the co-crystallized ligands (-6.9682 to -5.1109 Kcal/mole), respectively. Docking analysis revealed that the sulfonamide moiety fits well within the active sites of target enzymes, interacting with the Zn^{2+} ion, while the phenyl triazole tail forms hydrophilic and hydrophobic interactions with amino acid residues. These findings suggest that the target compound may exhibit selectivity to inhibit *h*CA IX and *h*CA XII isoforms.

Keywords
Solid tumors; Carbonic anhydrase; SLC-0111; Tail approach, and molecular docking studies



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1.Introduction

Cancer poses a significant worldwide health challenge, as it is responsible for millions of newly diagnosed cases annually and ranks among the top causes of death internationally [1]. It can manifest in numerous forms, affecting virtually any organ or tissue, and poses a significant global health challenge[2]. The development of cancer is often influenced by a combination of genetic predisposition, environmental factors, and lifestyle choices[3]. Another significant element contributing to malignancy is the decrease in oxygen levels within the solid tumor's microenvironment, leading to a state of hypoxia [4]. To adapt and thrive in such conditions, cancer cells employ glycolysis and increase the expression of specific enzymes to lower the external pH [5]. Among these enzymes, *h*CA IX isoform is upregulated by tumor cells in response to hypoxia, aiding these cells in acclimating to the acidic conditions induced by low oxygen levels, thereby advancing cancer cell growth [6–8]. On the other hand, *h*CA XII is excessively activated in various solid tumors like breast, lung, and cervical cancers [9,10]. These enzymes facilitate the reversible conversion between bicarbonate ions and carbon dioxide, utilizing zinc as a vital metal co-factor in the process that regulates the external pH [11,12]. On a molecular level, all human CA isoforms share a structurally conserved active site characterized by a cone-shaped pocket containing a zinc ion coordinated with three amino acid residues (His94, His96, and His119) and water [13]. The periphery of this active site consists of hydrophilic and hydrophobic regions, exhibiting variations in hydrophobicity and polarity across different *h*CA isoforms [14]. Consequently, *h*CA inhibitors (CAIs) incorporate a zinc-binding group (ZBG) essential for coordinating with the zinc ion in the active site [15,16]. Despite sulfonamides being the most effective *h*CAIs, they act non-selectively against nearly all *h*CA isoforms, leading to unintended side effects [17]. Given the substantial similarity in the active sites of CA isoforms, developing a selective inhibitor targeting specific diseases has proven challenging [18]. To address this selectivity issue, the "tail approach" has emerged as a promising strategy [19,20]. This approach involves introducing various substituted phenyl or heterocyclic structures onto the aromatic sulfonamide ring of *h*CAIs to interact with distinctive hydrophilic/hydrophobic residues in the peripheral regions of the isoform's active site [21]. Utilization of tail approach in the development of selective *h*CAIs have resulted in the identification of SLC-0111, marking the first instance of a selective CAI towards *h*CA IX isoform in clinical trial phases I/II, showing potential for treating patients with advanced solid tumor **Fig 1** [22]. Several analogs of SLC-0111 have been synthesized by replacing its 4-fluorophenyl tail with different chemical frameworks. Compound I was designed by replacing 4-fluorophenyl tail of of SLC-0111 with 5-(4-fluorophenyl)thiazole [23]. Similarly, Compounds II and III was prepared by replacing the tail of SLC-0111 with benzothiazole [24] and substituted 1,3,5-triazine moiety [25], respectively **Fig. 1**.

Inspired by these findings, this present study unveils the synthesis of a novel compound designed as a structural counterpart to SLC-0111. Our objective is to uncover novel and selective carbonic anhydrase inhibitors (CAIs), as illustrated in Fig. 2. Initially, we substituted the para-fluorophenyl tail in SLC-0111 with aryl triazole, resulting in the newly synthesized triazole-based analogue of SLC-0111.

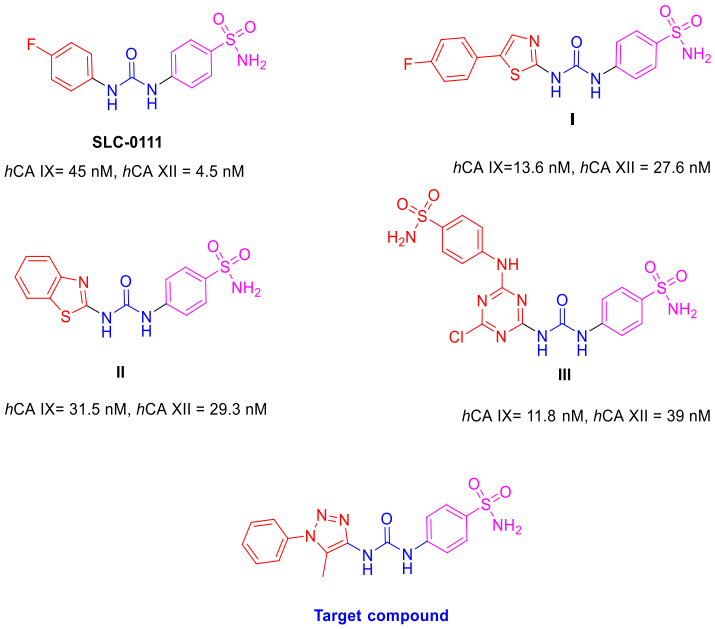


Figure 1. Chemical structures of SLC-0111, its reported analogues, and target compound

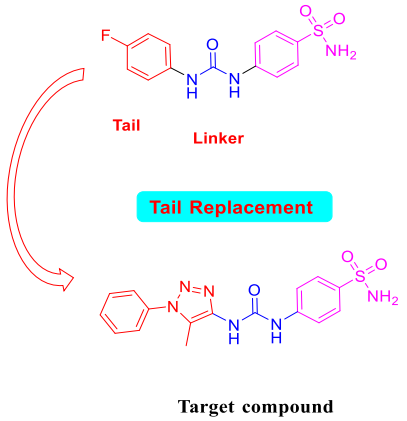


Figure 2. Design of 4-(3-(5-methyl-1-phenyl-1H-1,2,3-triazol-4-yl)ureido) benzenesulfonamide analogue of SLC-0111.

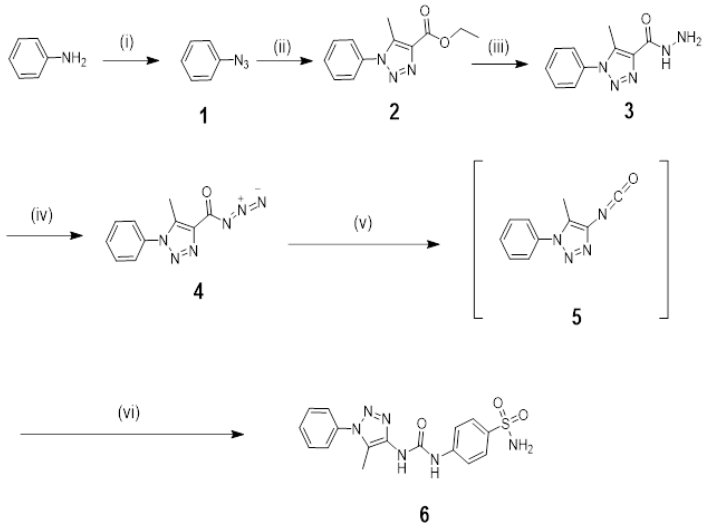
Results and discussion

Chemistry

Both compound **6** and its intermediates were prepared as outlined in **scheme 1**. The Phenyl azide **1** was prepared *via* diazotization of aniline with sodium nitrite in hydrochloric acid and further treatment with sodium azide affording intermediate **1** in a good yield [26]. Cycloaddition of phenyl azide 1 with ethyl acetoacetate in the presence of dimethylamine (10 mol %) in dimethyl sulfoxide (DMSO) at 65-70 C° afforded the phenyltriazole ester **2** in a good yield [27]. The hydrazide 3 was synthesized according to the reported procedure by treatment of

1,2,3-triazol-4-ester **2** with excess hydrazine hydrate in ethanol [28]. The hydrazide intermediate **3** was subjected to diazotization using $NaNO_2$ in the presence of hydrochloric acid. This was followed by treatment with sodium azide, resulting in the formation of phenyl triazole azide **4**. Subsequently, the compound underwent Curtius Rearrangement through refluxing in dry xylene, leading to the formation of the isocyanate intermediate **5**. Further refluxing of intermediate **5** with sulfanilamide in dry xylene resulted in the synthesis of the desired 1,2,3-triazole based sulfonamide **(Scheme 1).**

^{1}H NMR spectrum of compound **6** in DMSO-d_6 showed two singlets at δ 9.27 and 8.62 ppm for the two NH groups of urea linker, while the free NH_2 group appeared as singlet δ 7.74 ppm. Also, the methyl group revealed singlet at δ 2.26 ppm **Fig 3**. On the other hand, ^{13}C NMR spectrum of compound **6** showed characteristic signals at δ 153.38 ppm corresponding to the carbonyl group of urea moiety and δ 9.35 ppm indicating the presence of methyl group **Fig 4.**



Reagent and conditions: (i) $NaNO_2$, HCl, NaN_3 stirring 2 h; yield 81 %(ii) Ethyl acetoacetate, diethylamine, DMSO stirring at 70 C° for 2 h; yield 74 % (iii) Hydrazine hydrate 99%, absolute ethanol, reflux 3 h; yield 70 % (iv) $NaNO_2$, HCl, NaN_3 stirring 2 h; (v) Xylene, reflux 1 h; (vi) Sulfanilamide Xylene, reflux 6 h; yield 54 %.

Scheme 1: Synthesis of target compound **6**

2.2 Molecular docking studies within the active sites of hCA IX and hCA XII

Based on our design, molecular docking studies have been done to uncover the possible binding interactions of compound 6 within the active sites of hCA IX and hCA XII as expected molecular targets. The docking investigations were done using the X-ray structures for hCA IX and hCA XII (PDB IDs: 5FL4 and 4WW8, respectively) [29,30]. To verify the docking setup, the co-crystallized ligands of hCA IX and hCA XII proteins were re-docked into the active site of each respective enzyme. This self-docking validation process was conducted to evaluate the appropriateness of the docking protocol for subsequent docking studies. The results demonstrated the effectiveness of the docking protocol, as indicated by the small Root Mean Square Deviation (RMSD) values (less than 2 for both target proteins: RMSD value for 5FL4 = 0.3370 and for 4WW8 = 0.5647) and the ability of the docking poses to replicate the essential interactions observed between the co-crystallized ligand and the hot spots (Zn2+, Thr199, and/or Thr200) in the active sites of hCA IX and hCA XII. Once the setup was validated, it was utilized to investigate the binding mode of newly designed compound within the active sites of the different carbonic anhydrase isoforms, namely hCA IX and hCA XII. Docking studies of compound 6 revealed that benzenesulfonamide moiety fits well into the active sites of hCA IX and hCA XII with nitrogen atom coordinating the zinc ion. The SO2 group formed H-bond with amine acid Thr 200 for hCA IX and amine acid Thr 198 in case of hCA XII. Also, hybrid compound demonstrated a robust binding affinity for hCA IX and hCA XII isoforms, exhibiting higher binding free energy (ΔG) values (-6.9682 to -5.5453 Kcal/mole) compared to the co-crystallized ligands (-6.9682 to -5.1109 Kcal/mole), respectively, Table 1. Molecular docking analysis showed that the sulfonamide portion of the compound effectively fits within the active sites of hCA IX and hCA XII, interacting with the Zn2+ ion. Additionally, the phenyl triazole tail of the compound engages in both hydrophilic and hydrophobic interactions with amino acid residues (Figs 5, 6, 7, and 8). These findings suggest that the investigated compound has the potential to selectively target tumor-associated hCA IX and hCA XII isoforms.

Table 1: Energy scores and binding interactions of Co-crystallizes ligands and compound 6 and within the active sites of *h*CA IX and *h*CA XII.

#	Compound	Protein	Binding energy (kcal/mol)	Interacting Metal/ Residue
1	Co-crystallized ligand	*h*CA IX	-5.9430	Zn^{+2}, Thr A:200, Leu: A199, and hydrophobic interactions
2	Target compound	*h*CA IX	-6.9682	Zn^{+2}, Thr A:200, Leu: A199, Val 130, Gln 92, Leu 92, Arg 129, and hydrophobic interactions
3	Co-crystallized ligand	*h*CA XII	-5.1109	Zn^{+2}, Thr A:198, and hydrophobic interactions
3	Target compound	*h*CA XII	-5.5453	Zn^{+2}, Thr A:198, His 91, Leu 197, Ser 130 and hydrophobic interactions

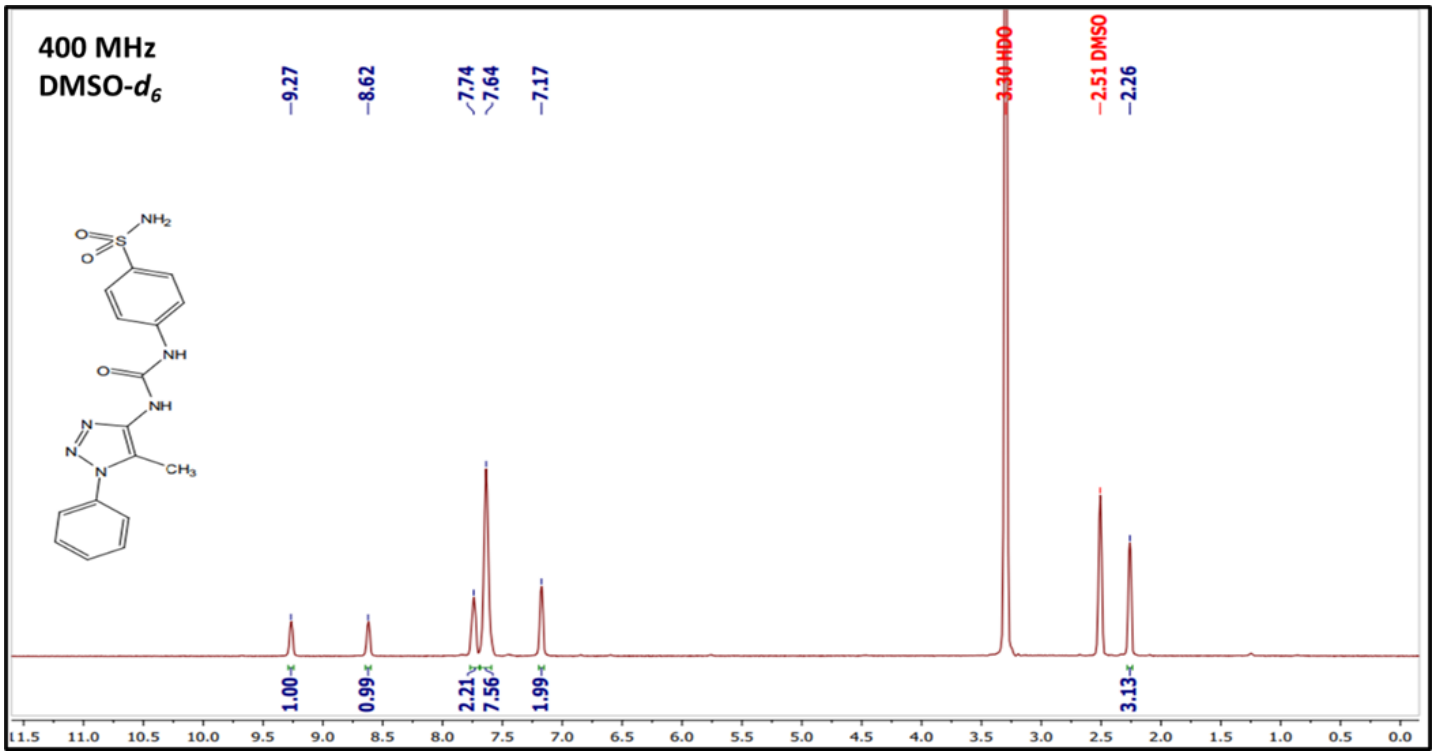


Figure 3. ^{1}H NMR of compound **6**

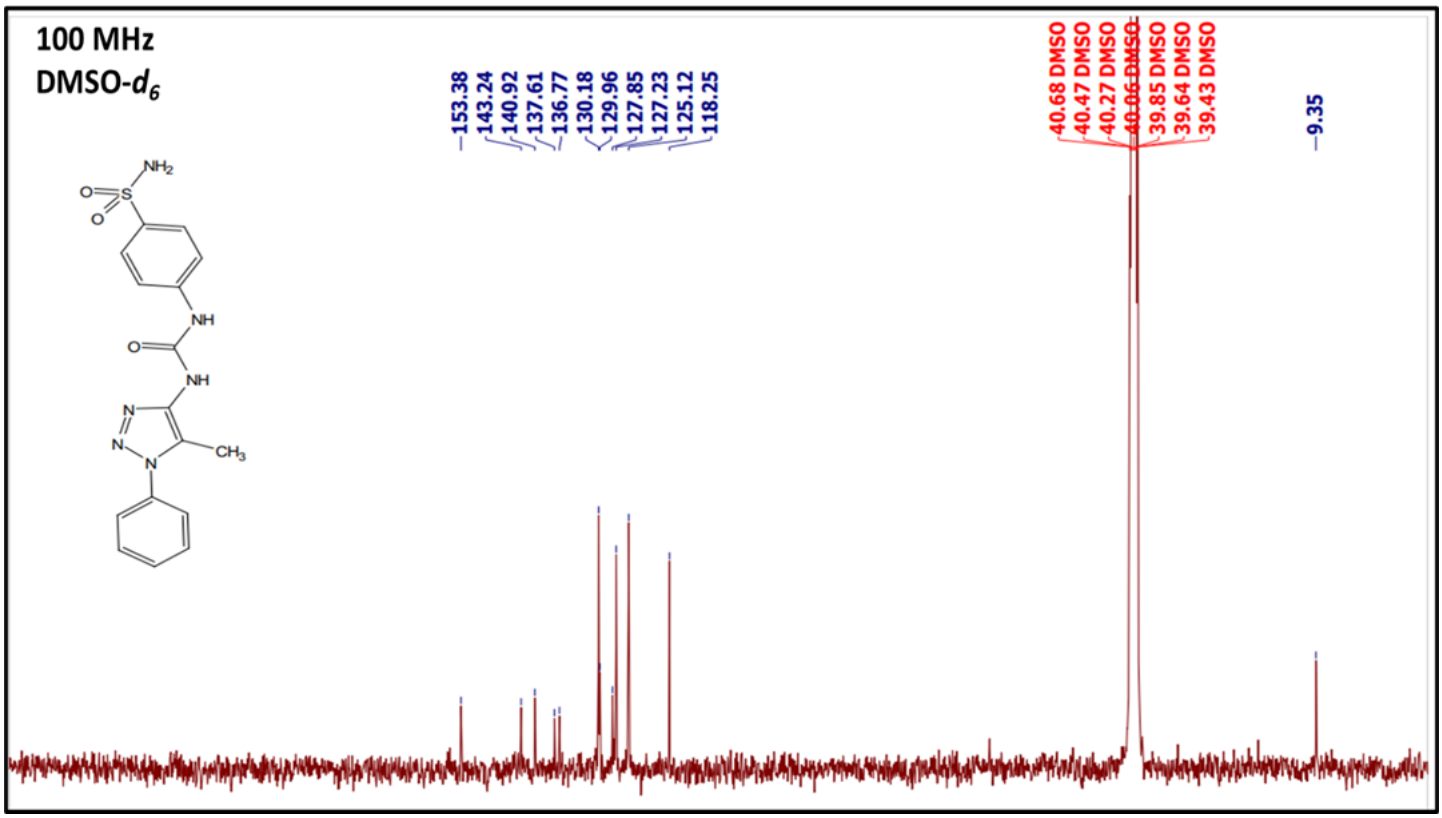


Figure 4. ^{13}C NMR for compound **6**

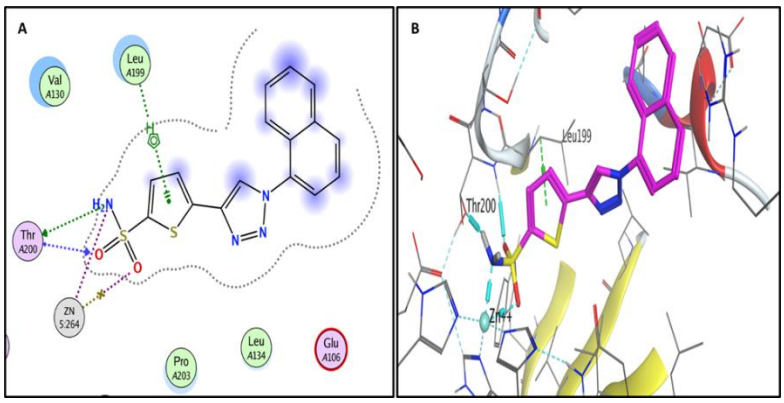


Figure 5. (A) 2D binding interactions of the co-crystallized ligand in the active site of *h*CA IX. (B) 3D binding interactions of the co-crystallized ligand in the active site of *h*CA IX.

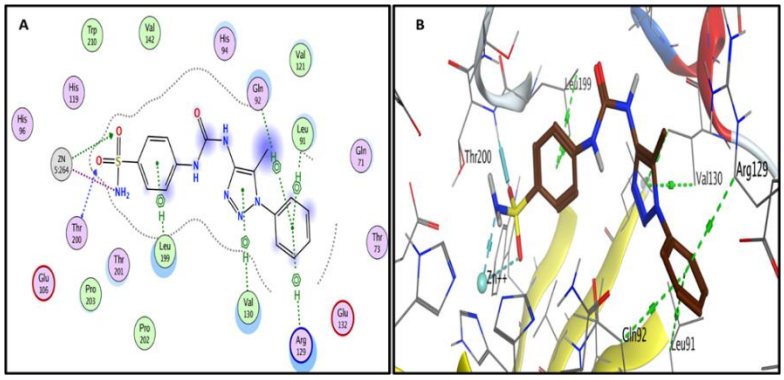


Figure 6. (A) 2D interaction map of compound 6 in the active site of *h*CA IX. (B) 3D interaction map of compound 6 in the active site of *h*CA IX.

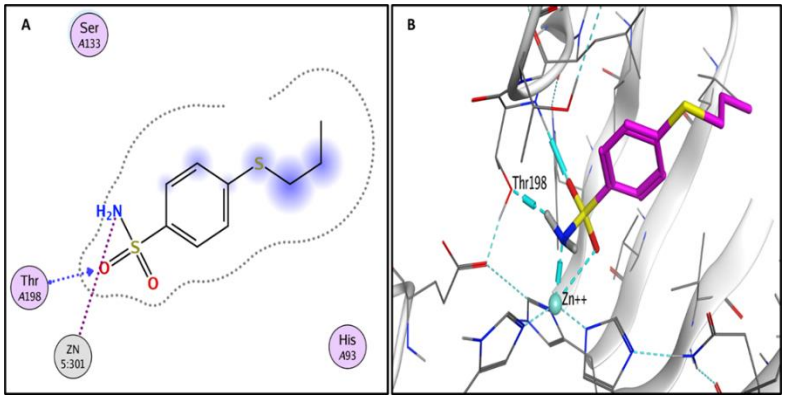


Figure 7. (A) 2D binding interactions of the co-crystallized ligand in the active site of *h*CA XII. (B) 3D binding interactions of the co-crystallized ligand in the active site of *h*CA XII.

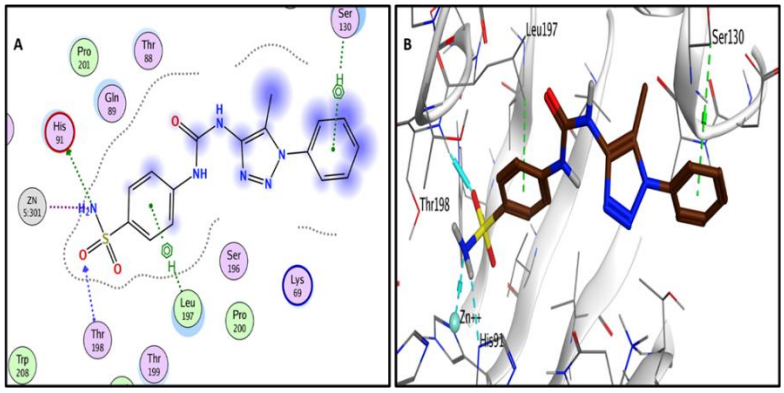


Figure 8. (A) 2D interaction map of compound 6 in the active site of *h*CA XII. (B) 3D interaction map of compound 6 in the active site of *h*CA XII.

Conclusion

In conclusion, our study focused on addressing the hypoxic conditions commonly observed in solid tumors. We developed a novel compound analogous to SLC-0111, a specific inhibitor of *h*CA IX, to explore its potential as an inhibitor for both *h*CA IX and *h*CA XII isoforms, which are associated with cancer. Molecular docking analysis revealed that the hybrid compound displayed strong binding affinity towards *h*CA IX and *h*CA XII, surpassing the binding free energy values of the co-crystallized ligands. The docking results indicated that the compound's sulfonamide moiety interacted effectively with the Zn^{2+} ion in the active sites of *h*CA IX and *h*CA XII, while the phenyl triazole tail formed interactions with amino acid residues through hydrophilic and hydrophobic interactions. These findings suggest that the compound may exhibit selectivity towards tumor-associated *h*CA IX and *h*CA XII isoforms. Further research and evaluation are needed to assess the therapeutic potential of this compound in hypoxic malignancies and its efficacy in clinical settings.

4. Experimental section

4.1. Chemistry

In this study, Thin-layer chromatography (TLC) was used to monitor the chemical reaction. Merck Grade-9385 precoated aluminum TLC plates with silica gel 60, were employed. UV light at 254 nm was applied to visualize the spots on the plates. Melting points were determined using a Stuart Electrothermal Melting Point Apparatus. The Bruker AM400 spectrometer, operating at 100 MHz for ^{13}C NMR and 400 MHz for ^{1}H NMR spectra, was used. The solvent DMSO-*d6* and the internal standard tetramethylsilane was utilized. intermediates **1** [26], **2** [27] , and **3**[28] were prepared as reported.

4.1.1 General procedures for synthesis of 4-(3-(5-methyl-1-phenyl-1*H*-1,2,3-triazol-4-yl)ureido)benzenesulfonamide 6.

A solution containing hydrazide intermediate **3** (1.5 g, 0.007 mol) and sodium nitrite (0.57 g, 0.008 mol) in hydrochloric acid was placed in an ice bath and stirred for 1 h. Then, a solution of sodium azide (0.54 g, 0.008mol) was added, and stirring continued for 1 h at room temperature. The obtained mixture was poured onto crushed ice. The solid that formed was filtered, air-dried, as 5-methyl-1-phenyl-1*H*-1,2,3-triazole-4-carbonyl azide **4**, which was used in the subsequent step as crude product. The intermediate azide **4** (1g, 0.003 mol) was heated under reflux in dry xylene for 1 h, followed by the addition of sulphanilamide (0.6g, 0.003 mol) to the xylene solution. The reaction mixture was heated under reflux for another 6 hs. After cooling to room temperature, the precipitated product was filtered, washed with ether, and recrystallized from ethanol to yield the desired compound **6** [31,32].

white powder; (0.7 g, 54 % yield); mp: 178-180 °C;^{1}H NMR (400 MHz, DMSO-d_6) δ 9.27 (1H, s, -N*H*-C=O), 8.62 (1H, s, -N*H*-C=O), 7.74 (2H, s, SO_2NH_2), 7.63-7.65 (5H, m, Ar-*H*), 7.17(2H, d, *J* = 7.74 Hz, Ar-*H*), 2.26 (3H, s, C*H*3); ^{13}C NMR (100 MHz, DMSO-d_6) δ 153.38, 143.24, 140.91, 137.61, 136.77, 130.18, 129.96, 127.85, 127.23, 125.12, 118.25, 9.35. Anal. Calcd. For $C_{16}H_{16}N_6O_3S$: C, 51.60; H, 4.33; N, 22.57; Found; C, 51.34; H, 4.11; N, 22.29.

4.2. Docking studies

The X-ray structures of the *h*CA IIXand hCA XII enzymes, with PDB IDs: 5FL4 and 4WW8, respectively, were accessed through the Protein Data Bank (PDB). The specific docking protocol employed in the study can be found in the Supplementary data section, where all the relevant details are provided.

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