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In Silico Assessment of Enaminone–Sulfanilamides as Potential Carbonic Anhydrase II Inhibitors: Molecular Docking and ADMET Prediction †

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Abstract: Carbonic anhydrases (CAs) are a group of zinc-containing enzymes involved in many physiological processes through their role in the maintenance of the equilibrium between bicarbonate and CO_2 levels. Human carbonic anhydrases (hCAs) are recognized as important drug targets due to their major implication in the development of diseases including cancer. Sulfanilamide derivatives have been widely studied and have shown remarkable efficiency in inhibiting carbonic anhydrases, with the presence of SO_2NH_2 in their structure. Therefore, the sulfonamide moiety is considered as the leading scaffold in the search for new hCA inhibitors. Moreover, the introduction of an enaminone to sulfonamide-based CA inhibitors showed an enhancement of inhibitory activity. In this context, we were interested in the in silico investigation of benzenesulfonamide derivatives containing β-enaminone that were synthesized from dicarbonyl compounds and sulfanilamide under microwave irradiation. The in silico assessment includes a molecular docking simulation against hCA II (PDB: 2AW1). The docked ligands showed good docking score values (−8.099 and −7.053 kcal.mol^{-1}), which indicates a good stability of the studied compounds within the active site. Further, significant interactions with the residues of the active site were observed, including metal coordination with Zn 262, an H-bond with Thr 199, and pi–pi stacking with the side chain of His94, which are considered as the key interactions for CA inhibition. A complementary in silico study that involved ADMET prediction was performed to learn more about the pharmacokinetic properties and the toxicity of the products in order to comprehend their ability to become drug-candidates.

Keywords: carbonic anhydrase; enaminone; benzenesulfonamide; molecular docking

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1. Introduction

Carbonic anhydrases are a group of zinc-containing enzymes present in the human organism. These metalloenzymes are known to be crucial in some of the different physiological reactions that help to maintain the harmony and good functioning of the human body by catalyzing the reversible transformation between CO_2 and H_2CO_3 [1]. Human carbonic anhydrase II (hCAII) is one of the large family of carbonic anhydrases that participates in many vital processes such as gluconeogenesis, lipogenesis, osteoclast differentiation, and acid–base balance [2]. A dysfunction in hCAII was recognized as a pathogenic factor engendering many diseases, including osteopetrosis and renal tubular acidosis [3].

Sulfonamides characterized by an SO_2NH_2 enchainment constitute the primary pharmacophore used in hCA inhibition. This efficient inhibition is due to the significant binding between the sulfonamide group and the zinc present within the active site of hCA [4].

The search for novel small molecules as hCA inhibitors is the primary occupation of researchers in the field of targeted therapy.

Our interest was focused on the in silico study of sulfonamide derivatives containing the enaminone moiety, including molecular docking against hCAII, as well as an ADMET predictive assessment of the stated derivatives in order to evaluate theoretically their suitability to become potential drug candidates.

2. Materials and Methods

2.1. Molecular Docking

A molecular docking study was carried out using the Schrodinger suite (glide) [5] and 3D visualization using Chimera software 1.11.2 [6].

2.2. ADMET Prediction

The ADME parameters and drug likeness of the synthesized compound were concluded using the SwissADME [7] and MolSoft [8] online servers. Moreover, a general prediction of the studied compound's toxicity was completed employing the ProTox-II online server [9].

3. Results and Discussion

3.1. Molecular Docking

In order to assess the binding mode of the investigated enaminone–sulfonamide derivatives inside the cavity of human carbonic anhydrase II, we performed a docking simulation using the existing XRD data of hCAII complexed with Valdecoxib (PDB: 2AW1).

Initially, a redocking was performed to obtain a valid docking protocol. In this context, protein was prepared using protein preparation wizard, waters were removed, and then a co-crystallized ligand was redocked using extra precision (XP). Results indicated an RMSD equal to 0.3176 Å, which corresponds to a valid value, indicating the reliability of the employed protocol. Superimposition of the docked reference ligand and the co-crystallized ligand is depicted in Figure 1.

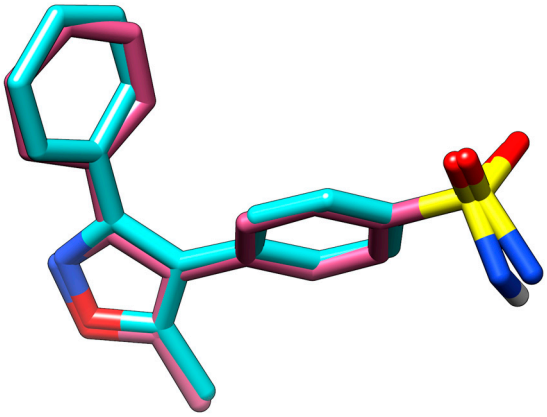
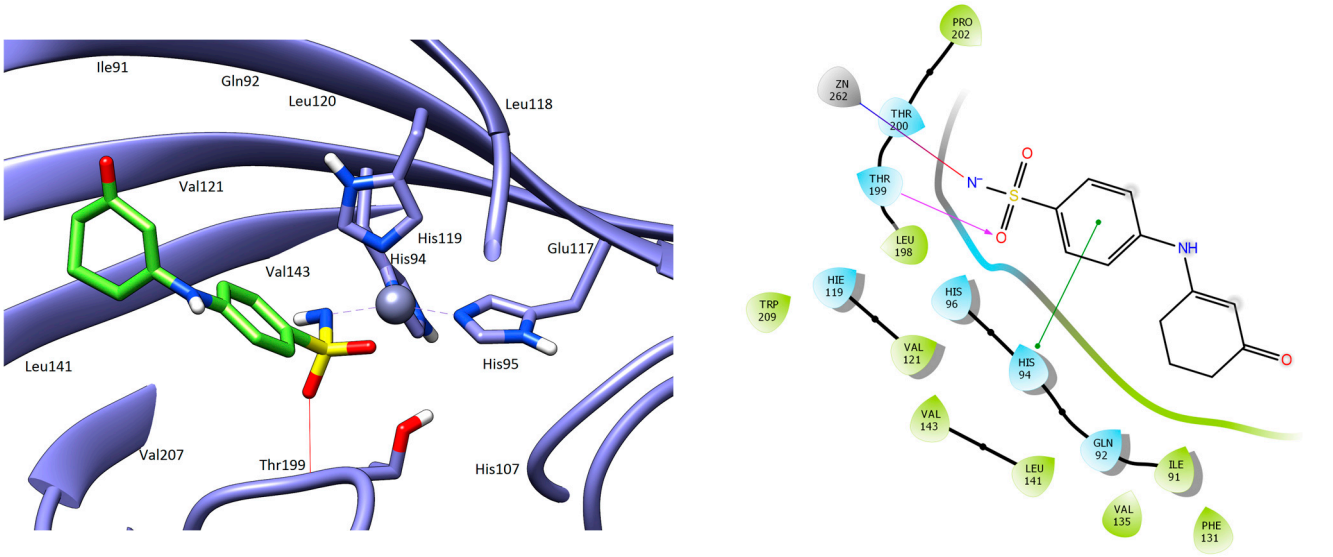


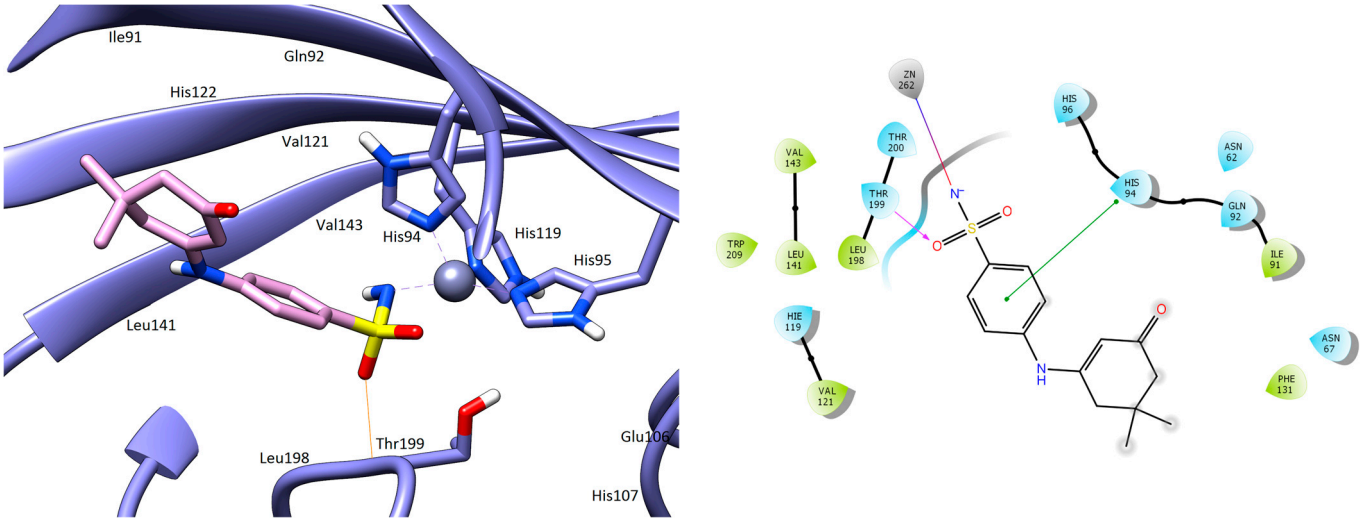
Figure 1. Superimposition of the docked reference ligand (pink) and the co-crystallized one (blue).

The investigated sulfonamide-based ligands showed great stability inside the hCAII enzyme's active pocket, exhibiting satisfactory docking scores equal to −8.099 and −7.053 kcal.mol^{-1}.

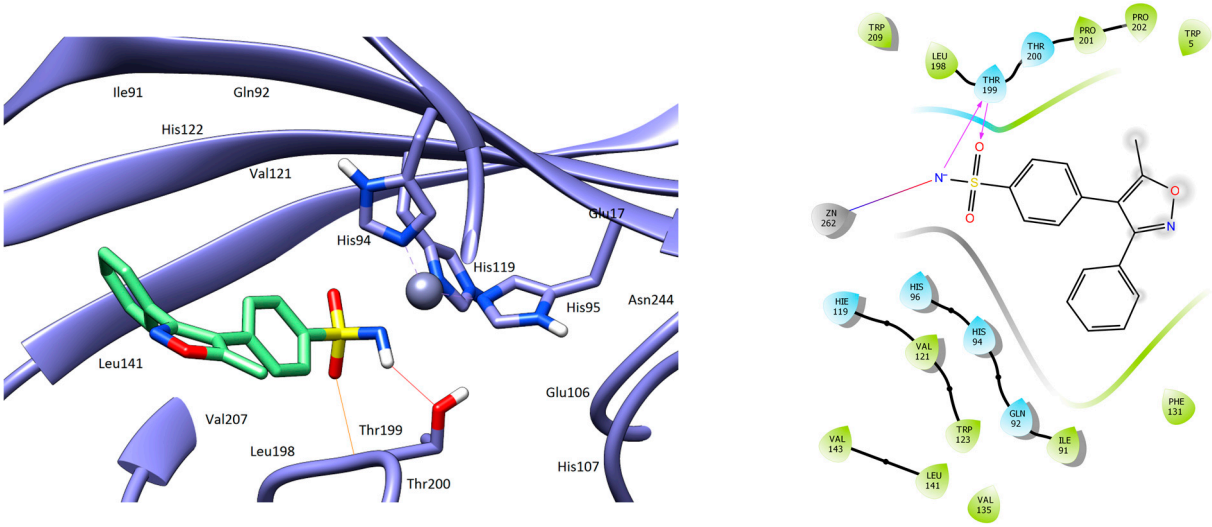
2D and 3D views of the investigated ligands in complex with carbonic anhydrase II were displayed in Figure 2. The studied compounds displayed significant interactions with the key residues of the active site, including a metallic bond with zinc and H-bond with Thr199, as well as a pi–pi stacking interaction with His94. Several hydrophobic interactions were observed, as shown in Table 1.



Compound a



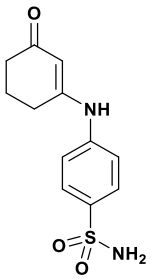
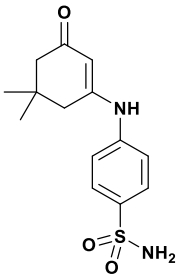
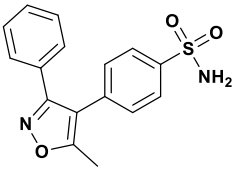
Compound b



Reference ligand

Figure 2. Three-dimensional (**left**) and two-dimensional (**right**) views of the ligand's interactions inside the cavity of hCAII.

Table 1. H-bonds and interactions of the studied compounds and the reference ligand.

Compound	Structure	H-Bonds	Hydrophobic Interactions	Docking Score (kcal.mol^{-1})
a		Thr199	Pro202, Leu198, Val121, Trp209, Val143, Leu141, Val135, Ile91, Phe131	−8.099
b		Thr199	Leu198, Val121, Trp209, Val143, Leu141, Ile91, Phe131	−7.053
Reference ligand		Thr199	Pro201, Pro202, Leu198, Val121, Trp209, Val143, Leu141, Val135, Ile91, Phe131, Trp5, Trp123	−9.001

3.2. ADMET Prediction

A potential drug candidate has to be subjected to many tests in order to evaluate its ability to enter the organism, including pharmacokinetic properties as well as toxicity levels.

A general prediction of the ADMET properties of the studied enaminone–sulfonamides was completed and the results are summarized in Table 2.

Table 2. Predicted pharmacokinetic properties, DLS, and toxicity of compounds **a** and **b**.

Properties	Compound a	Compound b
Molecular weight (g per mole)	266.32	294.37
Rotatable bonds	3	3
H-bond donor	2	2
H-bond acceptor	4	4
Violations	0	0
Log $P_{o/w}$ iLOGP	1.40	1.71
Log S ESOL	−1.99	−2.67
GI	High	High
BBB	No	No
Log Kp (cm/s)	−7.41	−7.00
Bioavailability score	0.55	0.55
TPSA (Å^2)	97.64	97.64
DLS	0.01	−0.07
Predicted LD50 (mg/kg)	5000	5000

Based on the criteria outlined in Table 2, the compounds under investigation adhere to Lipinski's rule of five [10], featuring a molecular weight below 500, four hydrogen bond

acceptors, two hydrogen bond donors, three rotatable bonds, and a LogP value of 1.40 and 1.71. The bioavailability radar provides additional insights into the compounds' drug-like characteristics, assessing factors such as polarity, solubility, saturation, lipophilicity, flexibility, and size. As depicted in Figure 3, the properties of the examined molecules fall within the acceptable range (indicated by the pink area). Furthermore, the drug likeness score (DLS) indicates the potential of the compound to serve as a drug candidate by comparing its attributes to those of known drugs. The DLS graphs in Figure 3 show that the DLS of compound **a** (0.01) and compound **b** (−0.07) are close to the drug area (blue plot).

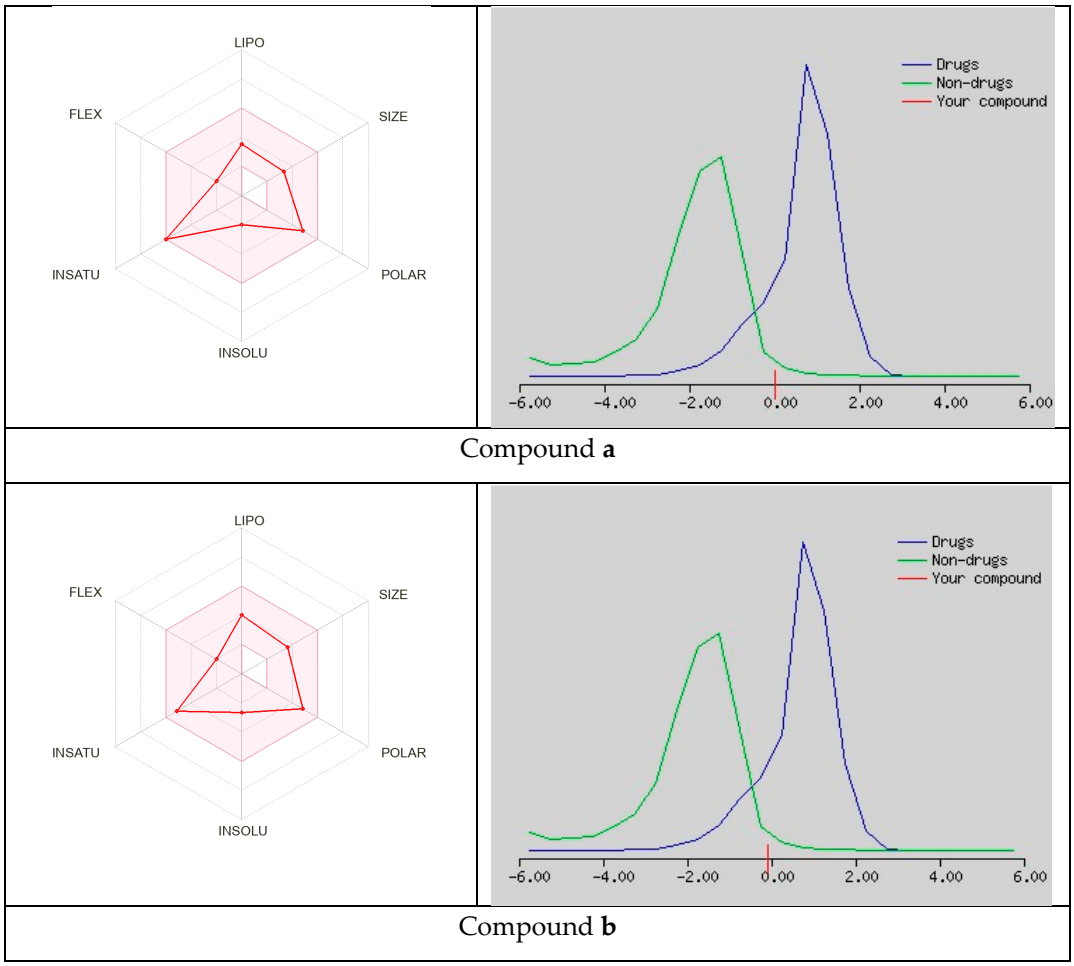


Figure 3. Bioavailability radar (**left**) and drug likeness estimation curve (**right**) of studied compounds.

4. Conclusions

Small sulfonamide-containing compounds bearing the enaminone moiety were subjected to in silico studies to evaluate their potential as drug candidates for human carbonic anhydrase II inhibition. The ligands demonstrated notable stability within the hCAII active site and formed interactions with key residues linked to their inhibitory activity. Additionally, the results of the ADMET predictions were encouraging, indicating that the compounds possess drug-like characteristics based on their predicted pharmacokinetic properties.

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Conflicts of Interest: The authors declare no conflicts of interest.

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