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

Yousra Ouafa Bouone [1], Abdeslem Bouzina [1,*], Rachida Mansouri [2] and Nour-Eddine Aouf [1]

[1] Laboratory of Applied Organic Chemistry, Bioorganic Chemistry Group, Department of Chemistry, Sciences Faculty, Badji-Mokhtar-Annaba University, Box 12, Annaba 23000, Algeria; yousra-ouafa.bouone@univ-annaba.dz (Y.O.B.); noureddine.aouf@univ-annaba.dz (N.-E.A.)
[2] Environmental Research Center (CRE), Annaba 23000, Algeria; r.mansouri@cre.dz (R.M.)
* Correspondence: abdeslem.bouzina@univ-annaba.dz;
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Abstract: Carbonic anhydrases (CA) are a group of zinc-containing enzymes involved in many physiological processes with their role in the maintenance of the equilibrium between bicarbonate and CO_2 levels. Human carbonic anhydrases (hCA) are recognized as important drug targets due to their major implication in the development of diseases including cancer. Sulfanilamide derivatives were widely studied and showed remarkable efficiency in inhibiting carbonic anhydrases; with the presence of SO_2NH_2 in their structure. Therefore, 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 the 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 was observed including a metal coordination with the Zn 262, an H-bond with Thr 199, and a pi-pi stacking with the side chain of His94, which are considered as the key interactions for a CA inhibition. A complementary in silico study that involves an ADMET prediction was performed to learn more about the pharmacokinetics properties and the toxicity of the products in order to comprehend their ability to become drug-candidates.

Keywords: carbonic anhydrase; enaminone; benzensulfonamide; 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 one of the different physiological reactions that help to keep 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 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 aptitude to become potential drug candidates.

2. Materials and Methods

2.1. Molecular Docking

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

2.2. ADMET Prediction

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

3. Results and Discussion

3.1. Molecular Docking

In order to assess the binding mode of 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 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.

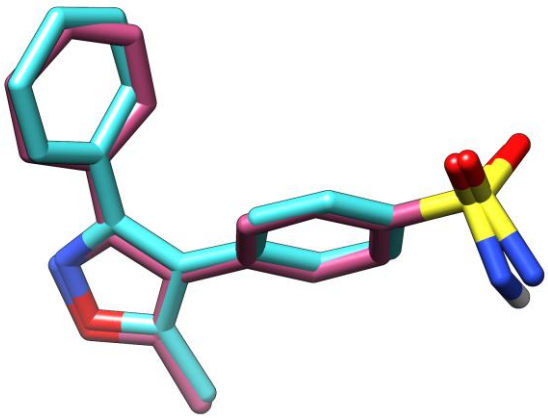
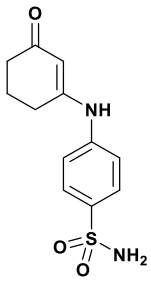
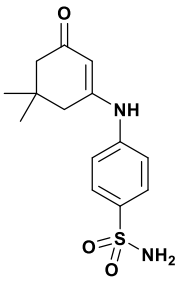
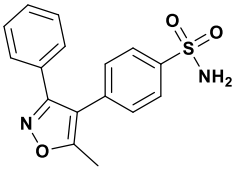


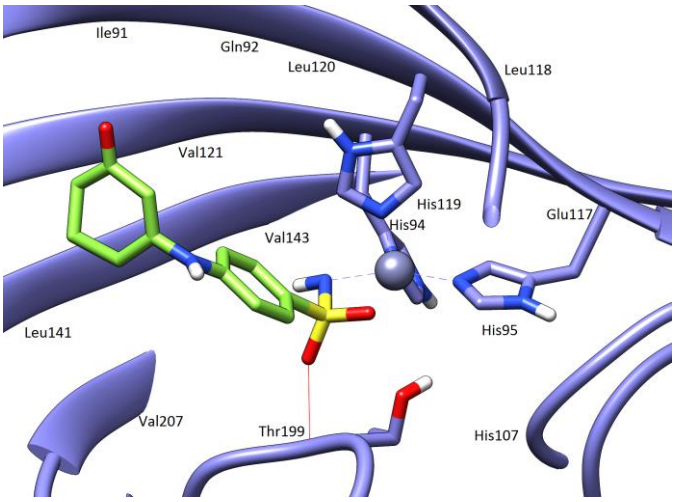
Figure 1. Superimposition of the docked reference ligand (pink) and the co-crystallized one (blue).

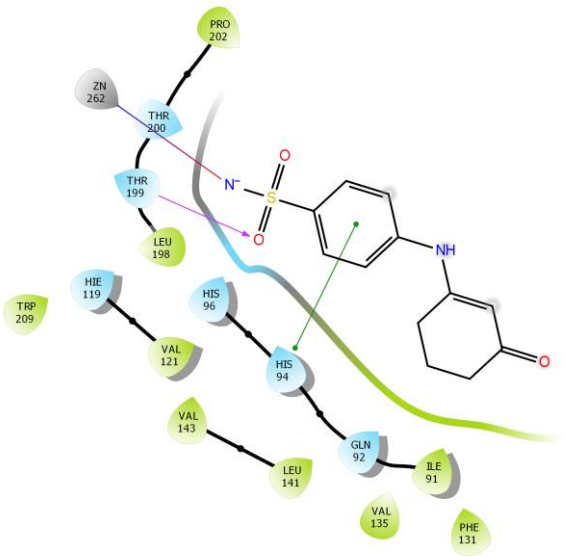
Investigated sulfonamide-based ligands showed great stability inside the hCAII enzyme's active pocket exhibiting satisfactory docking scores equal to −8.099 and −7.053 kcal.mol^{-1}.

Studied compounds displayed significant interactions with the key residues of the active site including a metallic bond with zinc and Hbond with Thr199, as well as a pi-pi stacking interaction with His94. Several hydrophobic interactions were observed as shown in Table 1.

Table 1. H-bonds and interactions of the studied compound 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





Compound a

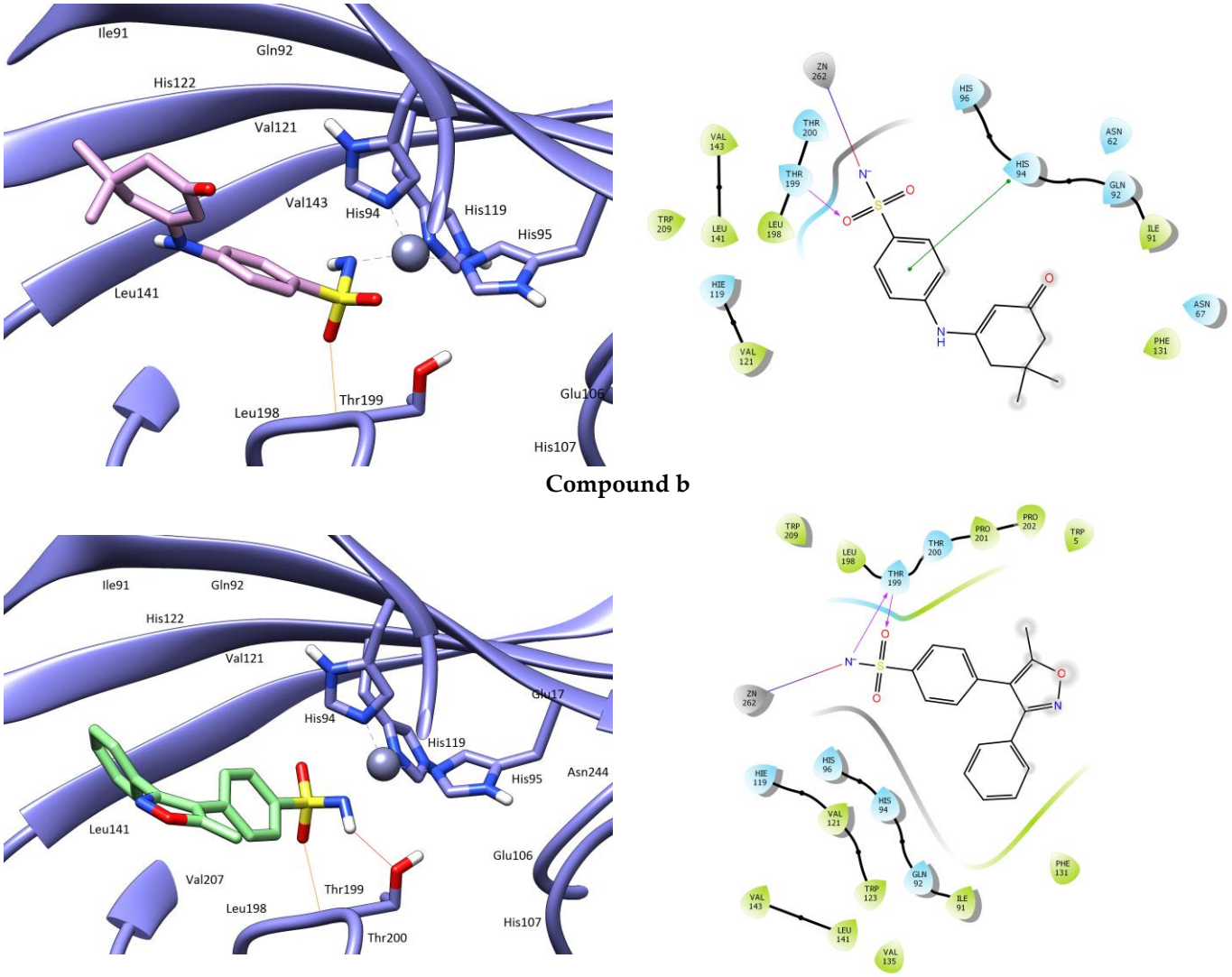


Figure 2. 3D (**left**) and 2D (**right**) views of the ligand's interactions inside the cavity of hCAII.

3.2. ADMET Prediction

A potential drug candidate has to be subjected to many tests in order to evaluate their ability to enter the organism including pharmacokinetics properties as well as the 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 pharmacokinetics properties, DLS score, and toxicity of compound **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 (Å²)	97.64	97.64
DLS score	0.01	−0.07
Predicted LD50 (mg/kg)	5000	5000

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

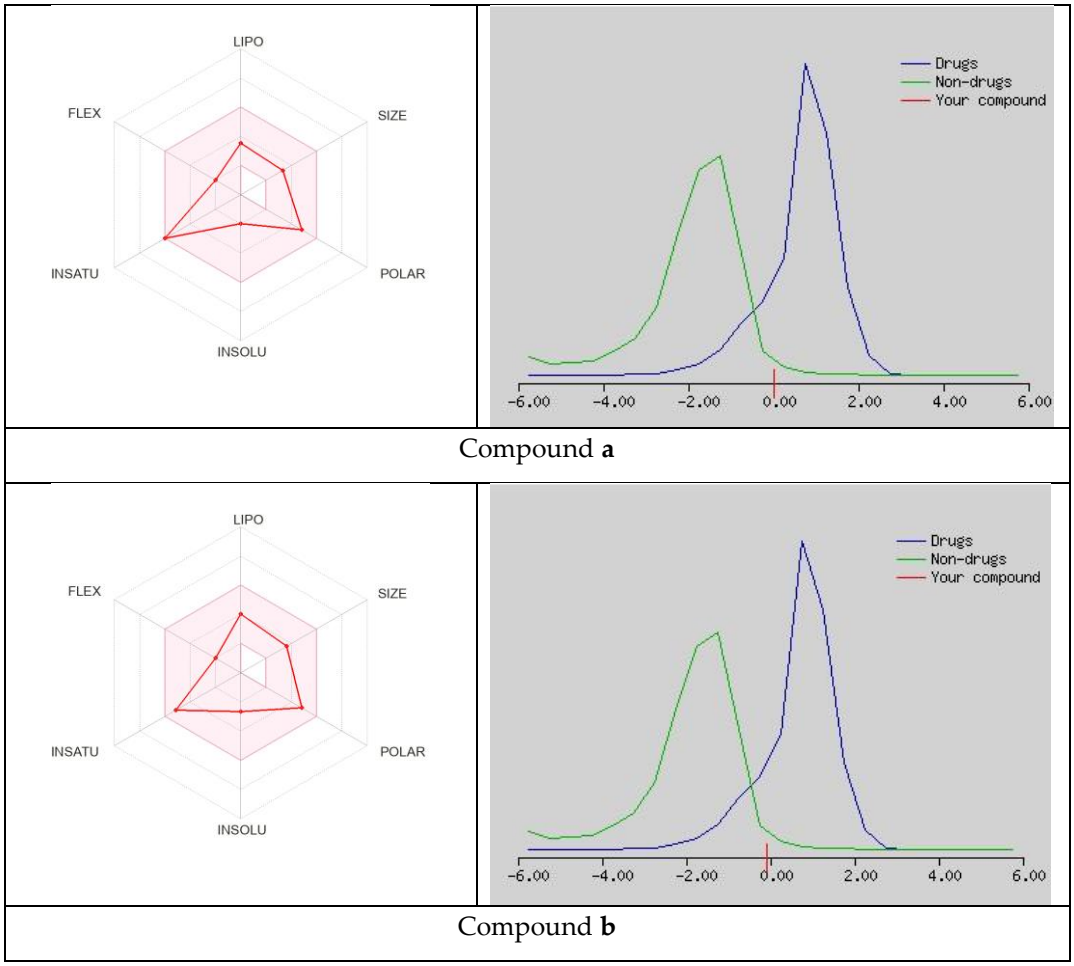


Figure 3. Bioavailability radar (**left**) and drug likeness estimation curve (**right**) of studied compound.

4. Conclusions

Small sulfonamides-containing compounds bearing the enaminone moiety was subjected to in silico studies to evaluate their potential as drug candidates for human carbonic anhydrase II inhibition. The ligand demonstrated notable stability within the hCAII active

site and formed interactions with key residues linked to its 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 conflict of interest.

References

1. Occhipinti, R.; Boron, W.F. Role of Carbonic Anhydrases and Inhibitors in Acid-Base Physiology: Insights from Mathematical Modeling. *Int. J. Mol. Sci.* **2019**, *20*, 3841.
2. Roumeliotis, S.; Roumeliotis, A.; Dounousi, E.; Eleftheriadis, T.; Liakopoulos, V. Biomarkers of vascular calcification in serum. *Adv Clin Chem*. **2020**, *98*, 91–147.
3. Alsharidi, A.; Al-Hamed, M.; Alsuwaida, A. Carbonic anhydrase II deficiency: Report of a novel mutation. *CEN Case Rep.* **2016**, *5*, 108–112.
4. Carta, F.; Supuran, C.T.; Scozzafava, A. Sulfonamides and Their Isosters As Carbonic Anhydrase Inhibitors. *Future Med. Chem.* **2014**, *6*, 1149–1165.
5. Friesner, R.A.; Banks, J.L.; Murphy, R.B.; Halgren, T.A.; Klicic, J.J.; Mainz, D.T.; Repasky, M.P.; Knoll, E.H.; Shelley, M.; Perry, J.K.; et al. Glide: A new approach for rapid, accurate docking and scoring. 1. Method and assessment of docking accuracy. *J. Med. Chem*. **2004**, *47*, 1739–1749.
6. Pettersen, E.F.; Goddard, T.D.; Huang, C.C.; Couch, G.S.; Greenblatt, D.M.; Meng, E.C.; Ferrin, T.E. UCSF Chimera--a visualization system for exploratory research and analysis. *J. Comput. Chem.* **2004**, *25*, 1605–1612.
7. Available online: https://www.swissadme.ch/ (accessed on).
8. Available online: https://www.molsoft.com/ (accessed on).
9. Available online: https://tox-new.charite.de/protox_II/ (accessed on).
10. Lipinski, C.A.; Lombardo, F.; Dominy, B.W.; Feeney, P.J. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Adv. Drug Deliv. Rev.* **2001**, *46*, 3–26.