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In silico study of five new sulfonamide derivatives bearing a thiazolidine-4-one moiety: targeting carbonic anhydrase IX

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Abstract

Molecular docking simulations were utilized to determine the binding affinities of five compounds produced. These compounds were IVa, IVb, IVc, IVd, and IVe. Chemicals derived from thiazolidin-4-one were designed to target cancer and human carbonic anhydrase IX (PDB code: 4M2V). These chemicals were designed to target humans. Our detailed sketching of the structure of the molecules was accomplished with the help of Chem Draw Ultra 12.0. To validate the compounds produced, the S. score and Rmsd values of the compounds were examined using the Molecular Operating Environment program. In contrast to acetazolamide, the proteins of the synthesized compounds had considerable binding affinities with the receptor active pocket, which suggested potential activity against cancer.

KEYWORDS

In silico, Cancer, Sulfanilamide derivatives, Thiazolidinone moiety, Carbonic anhydrase

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1. INTRODUCTION

Enzymes are crucial mediators in various biochemical processes that occur in living organisms. They are attractive candidates for therapeutic intervention due to their selectivity and exceptional efficacy in activating specific chemical reactions. The role that enzymes play in several diseases, including cancer, metabolic disorders, and infectious diseases, has led to an increase in the use of enzymes as possible pharmaceutical targets in recent years [1,2,3]. The term “cancer” refers to a broad range of diseases defined by the development of aberrant cells that can multiply uncontrollably, invade healthy tissue, and cause its destruction [4]. Now, second only to cardiovascular disease, cancer remains one of the world's top causes of mortality [5]. One of the biggest problems facing the healthcare system is the rising incidence of cancer treatment failure, which is caused mainly by tumors that are resistant to anti-cancer drugs [6]. Therefore, researchers require

innovative strategies to address intrinsic tumor cell heterogeneity, fixation of DNA damage, inactivation of drugs, change of drug targets, and suppression of cell death, as these factors significantly contribute to drug resistance [7]. Microenvironment-based tumor protection mechanisms seem more promising for drug targeting. In cancer research, the microenvironment plays a critical role in the survival and metastasis of cancer cells [8]. Hypoxia and acidity in the tumor microenvironment impact cancer biology. In most cases, hypoxia and acidosis promote the invasion, migration, and metastasis of cancer cells, which makes treating tumors much more difficult; hence, treatment approaches that interfere with these processes are desirable [9]. As a result, the carbonic anhydrase enzyme family, which controls intracellular pH, has been the center of extensive cancer research [10].

1.1. Carbonic anhydrase (CA)

CA is a family of widely distributed zinc enzymes that catalyze the reversible conversion of water (H_2O) and carbon dioxide (CO_2) into bicarbonate (HCO_3^-) and a proton (H^+) [11]. In humans, 15 isoforms of carbonic anhydrase enzymes differ in location and catalytic activity. These comprise the cytosolic CAs, CA I_III, CA VII, and CA XIII; the mitochondrial CAs, CA VA and CA VB; the secretory CA VI in saliva and colostrum; and the membrane-bound CAs, CA IV, CA IX, CA XII, CA XIV, and CA XV. Furthermore, three "CA-related proteins" proteins, CA VIII, CA X, and CA XI, are catalytically inactive forms of CA [12]. Interestingly, Carbonic anhydrase IX (CA IX) is overexpressed in many solid tumors and has minimal expression in many normal organs. This overexpression helps tumor cells proliferate, survive, and spread across the tumor microenvironment. As a result, CA IX has been confirmed as a promising target for cancer diagnosis and treatment [13]. CA IX is highly expressed in response to hypoxia in various human solid tumors, such as lung, colorectal, breast, and glioblastoma. It regulates tumor acidity, proliferation, and progression [14]. The overexpression of CA IX results in the proliferation of cancer cells, the initiation of the metastatic cascade, and a diminished response to chemotherapy. It has been demonstrated that targeting CA IX in malignancies that overexpress these indicators and inhibit their activity is therapeutically advantageous in managing tumors [15].

1.2. Human Carbonic Anhydrase (hCAs)

All catalytic hCAs coordinate zinc ions (Zn^{2+}), which are required for the hydration of carbon dioxide,

through a highly conserved inner binding pocket. As a result, most hCA inhibitors discovered so far include a zinc-binding group, often in the form of a sulfonamide [16]. Sulfonamides are as important as they are biologically active in pharmaceuticals [17]. Sulfonamides were initially widely used as chemotherapeutic agents and for preventive treatments across various diseases. Since 2005, they have gained considerable attention for their potential as anticancer treatments due to their ability to inhibit carbonic anhydrase [18]. Depending on the substituent groups made on the aromatic ring, Sulfonamide derivatives can form precise interactions within the characteristic enzyme bipolar structure, whether in the central active site or along the edges [19].

1.3. 4-Thiazolidinone

Within medicinal chemistry, heterocyclic compounds with five members, particularly those with several heteroatoms, have demonstrated various biological activity [20,21]. The one that has drawn the most interest over time is thiazolidinone, which has three different atoms: a sulfur atom at position 1, a nitrogen atom at position 3, and a carbonyl group at locations 2, 4, or 5 [22]. Thiazolidinone fragments are also commonly selected to modify lead compounds in anti-tumor drugs, so researchers are investigating numerous derivatives of thiazolidinone with varying substituents as potential anticancer drugs [23]. These derivatives may be able to fight cancer in many ways, such as by starting apoptosis, stopping the cell cycle, or producing reactive oxygen species (ROS). Thiazolidin-4-one-containing compounds efficiently inhibit several enzymes, including tubulin polymerization, HSP90, carbonic anhydrases, VEGFR2, EGFR, CDC25A HER-2, HDAC, BCL-2 protein, and protein/tyrosine kinases [24,25].

1.4. Aim of the work

This work aims to design some CAIs (carbonic anhydrase inhibitors) based on 4-thiazolidinone derivatives. Table 1 lists a series of target compounds identified by their compound numbers (IVa to IVe) and their corresponding substituents (R groups). Each R group represents a specific chemical moiety attached to the core structure of the compound, which can significantly influence the compound's chemical and physical properties.

In silico molecular docking studies will be performed to evaluate the binding affinity to the carbonic anhydrase enzyme. Subsequently, we will select the most potent compounds with strong enzymatic effects for further chemical synthesis.

The general structure of these compounds:

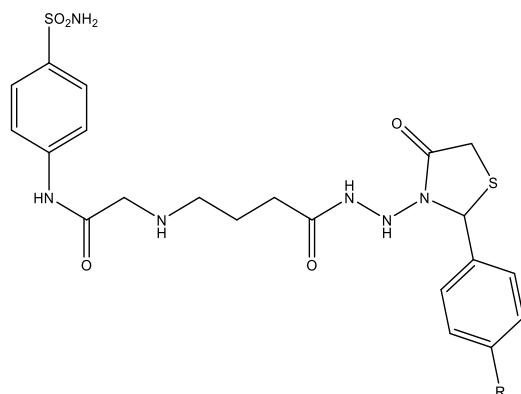


Table 1. Target compounds.

Compound No.	R
IV _a	N(CH ₃) ₂
IV _b	Cl
IV _c	NO ₂
IV _d	Br
IV _e	OH

2. METHODOLOGY

2.1. Chemical synthesis

Figure 1 demonstrates the sequential process employed to create sulfanilamide's target compounds (IV_a-IV_e). Each compound includes a distinct substituent (R group) linked to the core structure.

2.2. The system and software of the computer

The present investigation utilized an MSI system with 4.00 GB of random-access memory and Intel Core i3-2330M processors running at 2.20 GHz. Chem Draw Ultra 12.0 and MOE 2015 were both installed and configured.

2.3. Preparing Receptor and Ligands with the Molecular Docking Method

The docking process involves two steps:

1. Ligand preparation: The ligand molecular structures were accurately depicted Using Chem Draw Professional (12.0). The ligand was then protonated in a three-dimensional shape, the partial charge was added, energy was minimized, and the results were saved.

2. Protein preparation: The crystal structure of carbonic anhydrase IX (Protein data bank code: 4M2V) is downloaded into the Molecular Operational Environment (MOE 2015) via the PDB website to prepare the protein. The following steps are taken to prepare the target protein: We chose only the chains participating in the protein action and deleted other chains. We deleted small compounds. We also removed water molecules. Priority is given to establishing the active site, adjusting the potential of the protein atoms, and then introducing hydrogen obscures bonds. After feeding from the previously generated ligand into MOE from stored data, the docking process is carried out.

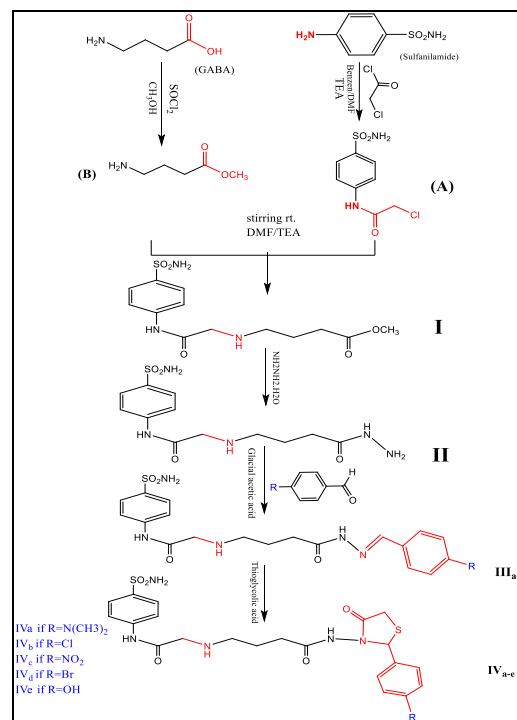


Figure 1. Synthesis of target compounds and their intermediates.

3. RESULTS AND DISCUSSION

3.1. Molecular Docking and Virtual Screening

Molecular docking determines the optimal binding of a ligand to an active site on a target. We used the MOE in the study because it provides a detailed graphical representation of ligand positions and interactions with receptor-binding residues, making it easier to visualize, characterize, and assess protein interactions with ligands [26]. Carbonic anhydrase IX has been difficult to yield, purify, and crystallize as a transmembrane protein for

SBDD. On the other hand, crystallizing and producing the comparable cytoplasmic-soluble carbonic anhydrase II isoform is simple [27]. The molecular operating environment demonstrates the selective binding of the proposed compounds to the CA IX enzyme, occupying the identical main active site as acetazolamide [28]. Analyzing the compound's inhibitory effect and the degree of similarity between amino acids that interact on identical active sites is necessary. It is shown in Table 2, which provides a comprehensive overview of the interaction parameters for the final products IVa, IVb, IVc, IVd, and IVe. It includes the S-score, Rmsd values and identifies the primary amino acids involved in these interactions. These parameters illustrate the binding affinity and structural alignment between the synthe-

sized compounds and their target proteins. These criteria can be found in S. scores and the root mean square deviation (rmsd) values, which measure the average interatomic distance between the ligand atoms and the target site for the anti-cancer compound. When the results show improved binding energy (S.score) and lower RMSD values, it means optimum posture. All of the synthesized (IVa-IVe) compounds show s. score better than the reference (acetazolamide), and this means a better inhibitory effect that may be attributed to extra binding with important amino acids in the carbonic anhydrase active site. They had S. score values of -8.8, -9.1, -8.55, -9.16, and -8.6, respectively, and rmsd values of 1.44, 1.9, 1.7, 1.9, and 1.7, respectively. As shown in Table 2.

Table 2 shows the S-score, Rmsd, and primary amino acids participating in the final products IVa, IVb, IVc, IVd, and IVe interaction. Threonine199 (Thr199), Zinc 301 (ZN301), Threonine200 (Thr200), Histidine64-94-96-119 (His64-94-96-119), Leucine198 (Leu198), Asparagine62 (Asn62), Glutamine67 (Glu67) and Tryptophan5 (Trp5).

Compound Name	R group	S-score	Rmsd	No. of binding sites	Binding amino acids
Acetazolamide	-----	-6.5	1.66	5	Zn301, Thr199, Thr200, His96, His119
IVa	N(CH ₃) ₂	-8.8	1.44	7	Zn301, Thr199, Leu198, Gln92, Asn62, His96, His119
IVb	Cl	-9.1	1.9	6	Zn301, Thr199, Leu198, Trp5, His96, His119
IVc	NO ₂	-8.55	1.7	6	Zn301, Thr199, Leu198, Trp5, His96, His119
IVd	Br	-9.16	1.9	10	Zn301, Thr199, Leu198, Gln67, Gln92, Trp5, His64, His94, His96, His119
IVe	OH	-8.68	1.7	8	Zn301, Thr199, Leu198, Gln92, His64, His94, His96, His119.

3.2. Discussion of the Docking Result

The active site of human carbonic anhydrase IX comprises a large cone-shaped cavity formed by a hydrophobic and a hydrophilic portion. Within the cavity of this enzyme, there is a catalytic cleft. Inside this cleft is zinc, acting as a cofactor. Three histidine residues, His94, His96, and His119, coordinate the zinc ion, stabilizing its positive charge and positioning it for catalysis. Threonine 199 is located near the active site and is involved in maintaining the structural integrity of the enzyme. It may also play a role in substrate binding and stabilization of the transition state during catalysis. As a result, the compounds should bind to zinc as well as Thr199 to provide inhibition to carbonic anhydrase IX. Additional binding with other amino acids such as Leu198, Gln67, Gln92, Trp5, and Asn 62 contributes to enhancing the inhibitory activity of

the synthesized compounds as these amino acids may be involved in substrate binding and participate in interactions with other nearby residues, assisting in maintaining the proper conformation of the active site cavity and all these amino acids are included in Table 2.

Acetazolamide is a valuable reference, a well-known and extensively studied carbonic anhydrase inhibitor. Moreover, it shares the same pharmacophore as our studied compounds. Figure 2 illustrates the docking simulation of Acetazolamide with HCA IX, utilizing (PDB code 4M2V). In this simulation, A represents the 2D structure, while B shows the 3D structure of the ligand-protein interaction. In Figure 2, Acetazolamide is depicted binding specifically to zinc and the amino acid residues threonine 199, threonine 200, and histidine within the active site of HCA IX.

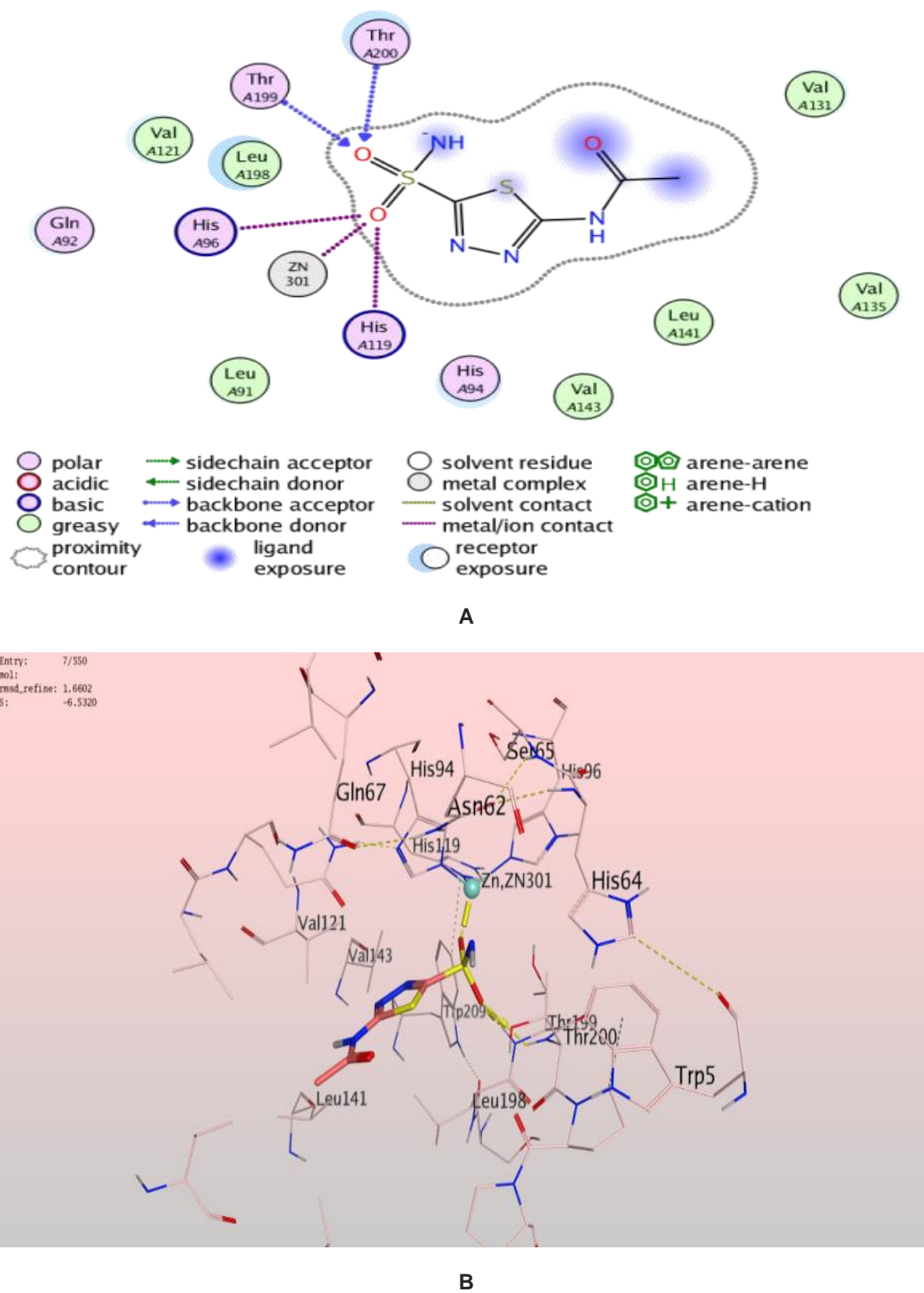


Figure 2. Docking stimulation of reference ligand (Acetazolamide) with HCA IX (PDB code: 4M2V). Where A represents 2D structure, B represents 3D structure.

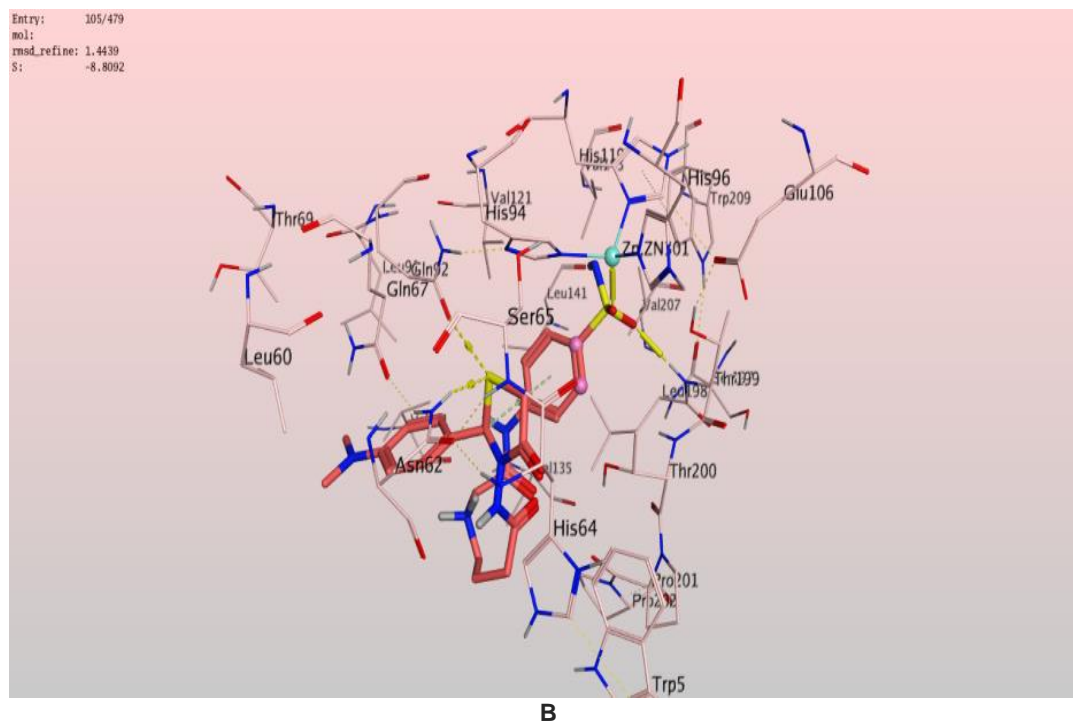
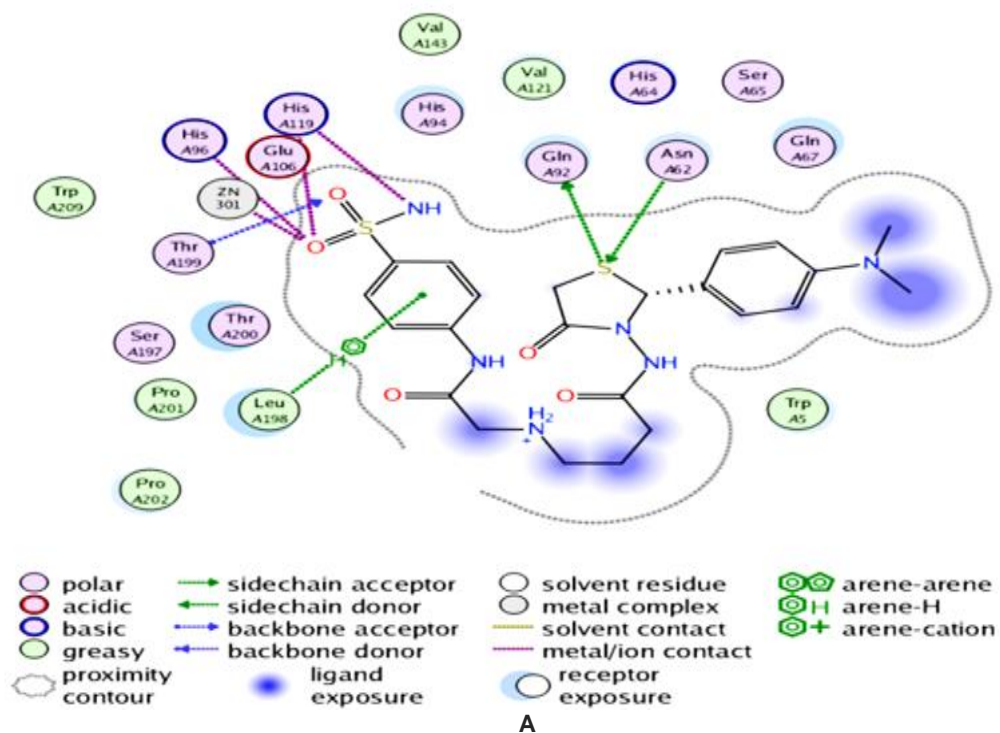


Figure 3. Docking stimulation of compound IVa with HCA IX (PDB code: 4M2V). where A represents 2D structure, B represents 3D structure.

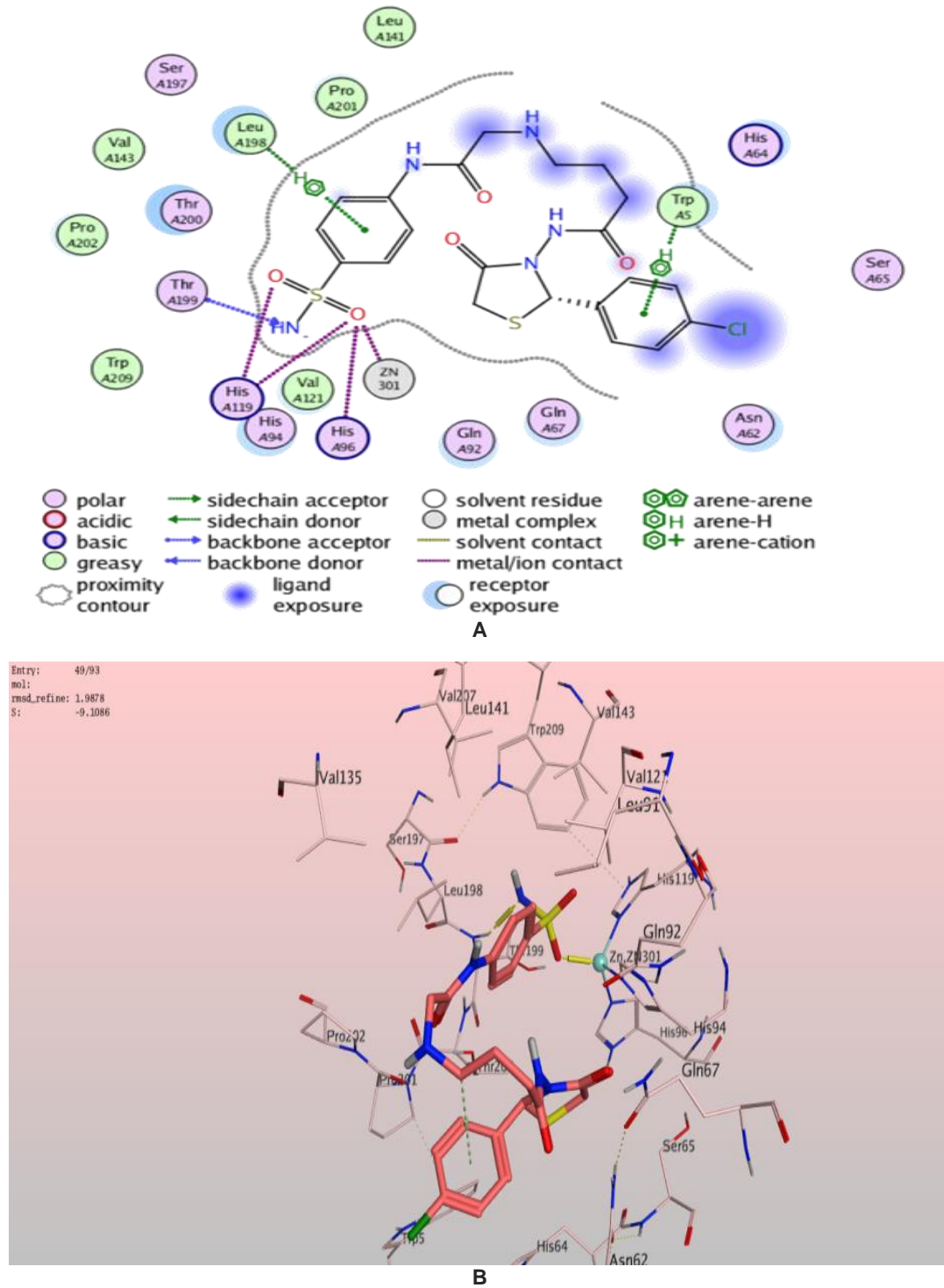


Figure 4. Docking result of stimulation IVb with HCA IX (PDB code: 4M2V). where A represents 2D structure, B represents 3D structure.

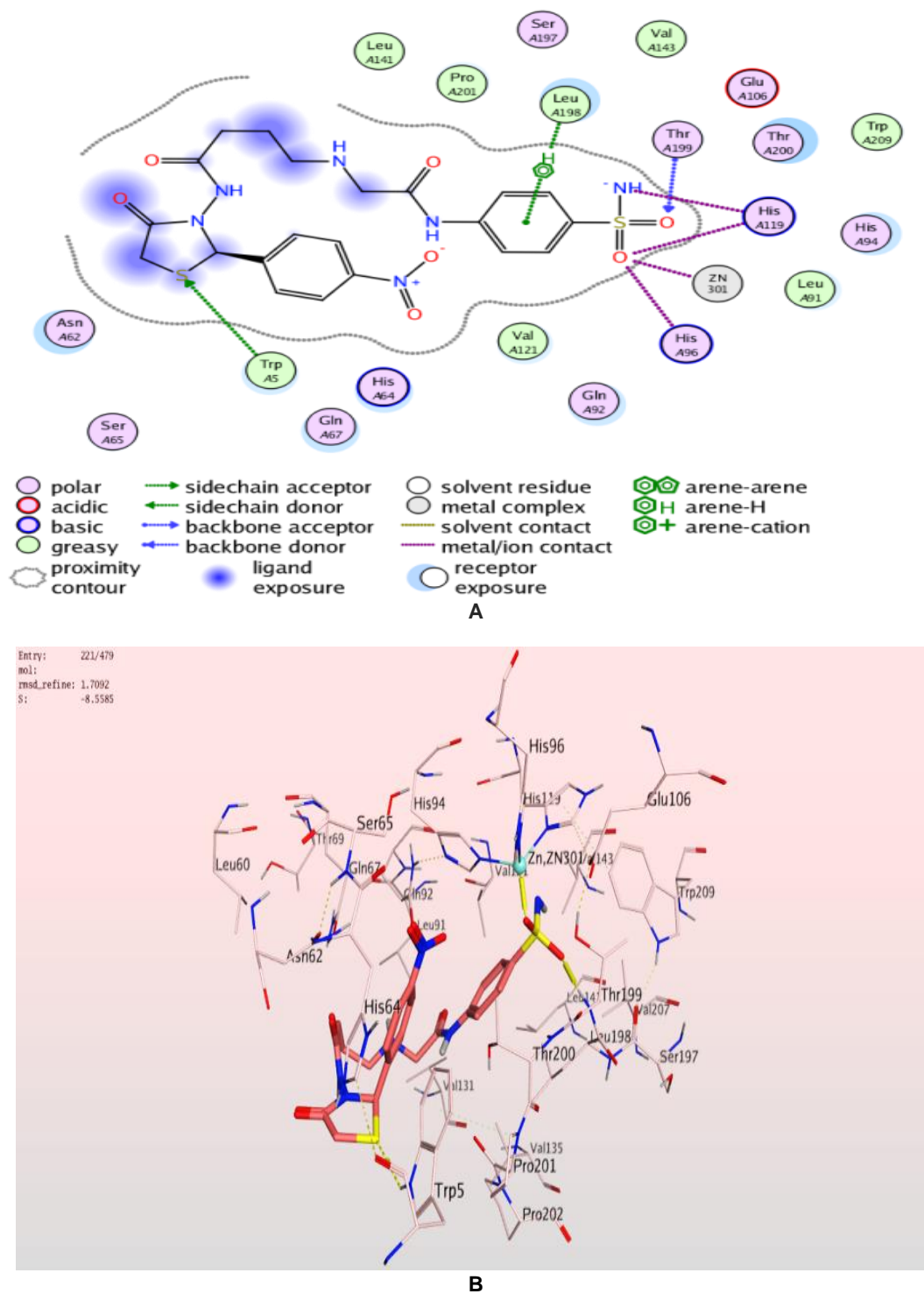


Figure 5. Docking stimulation of compound IVc with HCA IX (PDB code: 4M2V), where A represents 2D structure, B represents 3D structure.

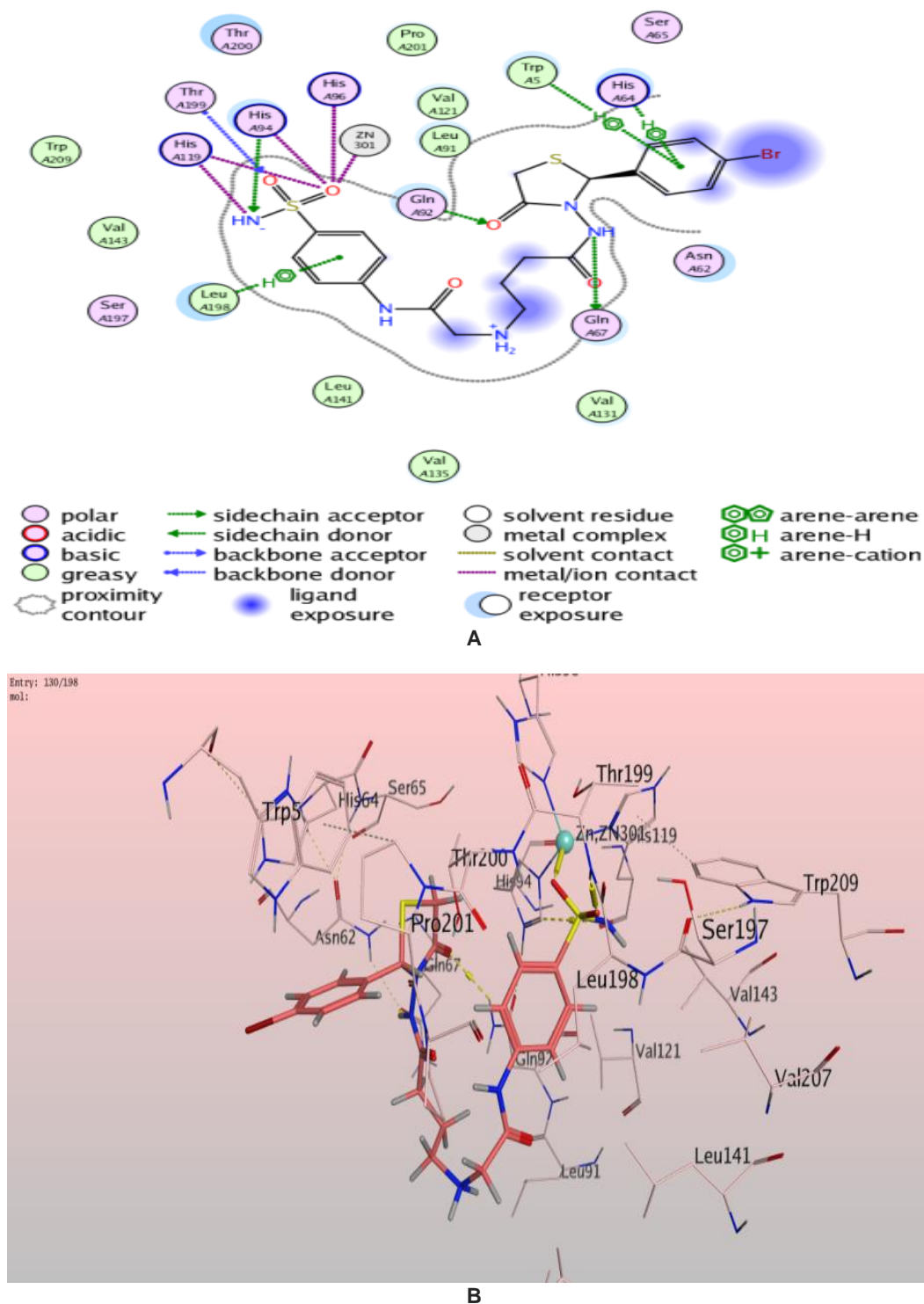


Figure 6. Docking stimulation of compound IVd with HCA IX (PDB code: 4M2V). where A represents 2D structure, B represents 3D structure.

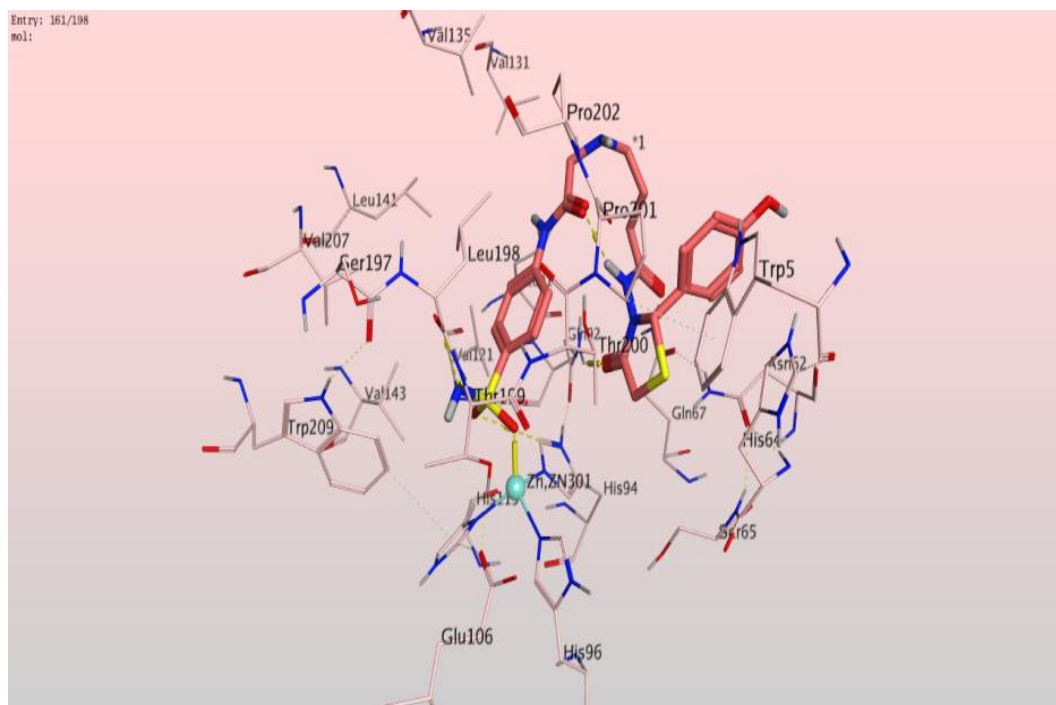
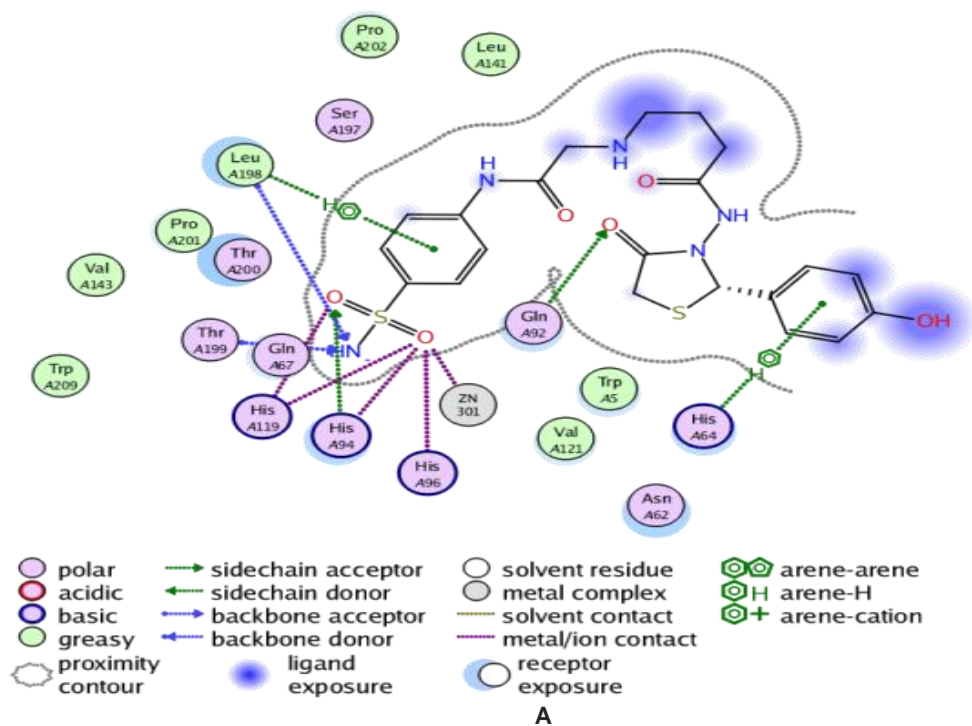


Figure 7. Docking stimulation of compound IVe with HCA IX (PDB code: 4M2V). where A represents 2D structure, B represents 3D structure.

Figures 3-7 depict the docking simulations of compounds (IVa-IVe) with HCA IX, utilizing (PDB code 4M2V). In each Figure, A represents the 2D structure, while B represents the 3D structure of the ligand-protein interactions.

Every sulfonamide derivative establishes zinc and a hydrogen bond with the essential amino acid Threonine199. In addition, Van der Waals interactions were also examined, as they are crucial for inhibiting enzymes. The Van der Waals interaction exists between all derivatives and HIS119. Figure 3 illustrates the docking simulation of compound IVa with HCA IX, revealing a favorable RMSD value of 1.44. The dimethylamino substituent on IVa facilitates its precise positioning within the CA IX active site. Particularly noteworthy is the interaction between the thiazolidinone ring of IVa and Asn62, a residue crucial for substrate binding in CA IX. This interaction likely enhances IVa's affinity and specificity for the enzyme, underscoring its potential as an effective CA IX inhibitor.

Figure 4 displays the binding interaction of compound IVb with CA IX. This Figure shows the additional binding of IVb with Trp5, which is essential for stabilizing the substrate within the Carbonic anhydrase IX active site. This additional binding may be due to the IVb high S.score of -9.1.

IVc demonstrates additional binding interactions of its thiazolidinone moiety with key amino acids, notably Trp5, within the active site of carbonic anhydrase IX. These interactions are depicted in both 2D and 3D representations in Figure 5.

Figure 6 illustrates the 2D and 3D binding interactions of compound IVd with the active site of CA IX. Compound IVd exhibits the highest S-score of -9.16, indicating strong binding affinity. This high S-score may result from additional hydrogen bonding with Gln67 and Trp5, essential for substrate stabilization and catalytic activity in CA IX. A bromine (Br) substituent may further enhance the orientation of IVd within the receptor pocket.

Finally, IVe exhibits additional binding of the thiazolidinone moiety with important amino acids Gln92 in the active site of CAIX. Inhibition of Gln92 in CAIX disrupts substrate orientation and active site stability, thereby reducing the enzyme's catalytic efficiency and potentially impairing cancer cell survival. The 2D and 3D binding of compound IVe with the CA IX active site is shown in Figure 7.

4. CONCLUSION

This study aimed to create and assess the *in silico* carbonic anhydrase inhibitor activity for derivatives of sulfonamides, including thiazolidinone moiety. We investigated the anticancer activity of our produced compounds against the enzyme carbonic

anhydrase IX using the docking results in MOE. Relative to acetazolamide, most compounds exhibited a higher affinity for interacting with target proteins. The most promising compounds are IVb and IVd.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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