ORIGINAL ARTICLE

CONTENTS

In silico study of new isatin- sulfonamide derivatives as carbonic anhydrase inhibitors

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ABSTRACT

Aim: To evaluate compound I, II, III, and IV's anticancer properties that have just been produced. These substances were created with the specific purpose of targeting solid tumors' carbonic anhydrase enzyme.

Materials and Methods: The chemical synthesis involved the use of 4-aminobenzenesulfonamide, Ethyl 4-aminobenzoate, isatin and its derivatives, absolute ethanol, DMF, glacial acetic acid. Docking studies were conducted using the MOE software program version 2015.10.

Results: Since acetazolamide and the sulfanilamide group shared the same pharmacophore, they were chosen. When compared to acetazolamide, compounds II and III produced a maximum score and an irreversible relationship.

Conclusions: Using the Molecular Operating Environment (MOE) software, the binding model and two values the RMSD and S.score—are computed for newly synthesized compounds. When compared to acetazolamide, the theoretically generated compounds showed promise results with these proteins and good binding affinities with the receptor active pocket (S. score: - 6.89, -7.12, -6.75).

KEY WORDS: in silico, cancer, carbonic anhydrase inhibitor, sulfonamide, isatin

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INTRODUCTION

As the leading cause of death worldwide and a major impediment to efforts to extend life expectancy, cancer remains a major global health concern. In 112 out of 183 countries, prior to reaching 70 years old, cancer is among the most common causes of death according to data from (WHO) for 2019. Furthermore, in 23 other nations, it ranks as the third or fourth most common cause of death [1-2]. Antitumor medication resistance in malignant cells is primarily accountable for the increased incidence of cancer treatment failure, creating new challenges for the healthcare system [3]. The discovery of novel treatments is required due to the issues with significant toxicity, drug resistance, and poor of selectivity with current chemotherapeutic medications [4]. Bicarbonate ion is produced reversibly by zinc-containing metallo enzymes known as carbonic anhydrases (CAs) [5]. All human CAs (hCAs) are members of the α-class, and humans have at least 15 different (CA) isoforms with varying molecular characteristics, tissue distribution, and subcellular localization [6]. Human cells currently express twelve α family catalytically active (CA) isoforms [7]. Since (hCA) XII expression limits in normal tissues and plays a critical role in pH regulation in a number of cancers (including breast, brain, colorectal, and others), this isozyme has gained interest as a target for antineoplastic therapy development [8]. The most researched class of (hCA) inhibitors (CAIs) is the sulfonamides and related bioisosteres, such as sulfamates and sulfamides, which have been used clinically for more than 70 years to treat obesity, glaucoma, and epilepsy as well as acts as diuretics [9]. Many structurally unique sulfonamide derivatives have finally been found to exhibit strong anticancer activity both in vivo and in vitro [10]. Medicinal chemists are interested in heterocyclic compounds because of their unique chemical properties and range of biological activity [11]. Its possible use as a treatment for a variety of diseases, such as cancer, has been studied [12]. Several naturally occurring alkaloids with indole as their fundamental ring have been found to be therapeutically active drugs, indicating that the indole nucleus is a particularly active nucleus in the pharmacy sector [13]. Isatin's nucleus, sometimes referred to as indole quinone or indanedione, may be viewed as a preferred scaffold for the creation of physiologically active substances [14]. The isatin scaffold could be decorated to produce a variety of biological

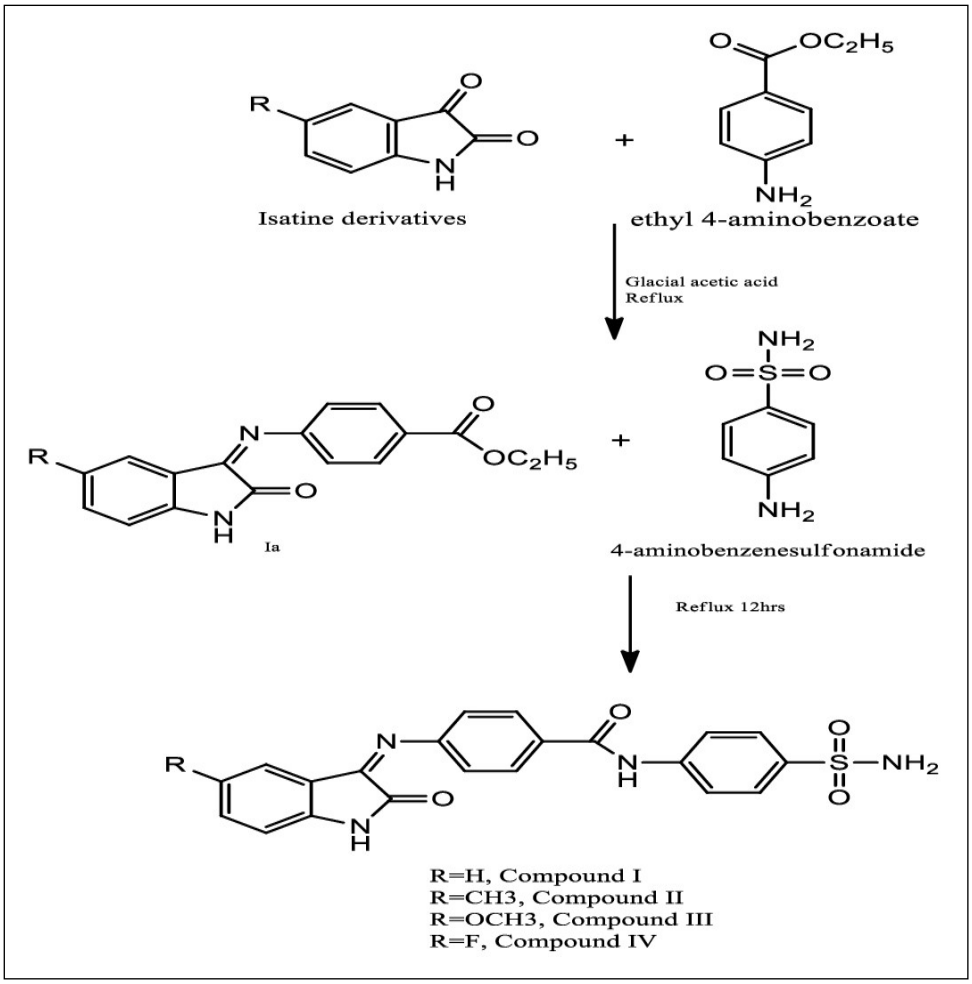

Fig.1. Synthesis of intermediate and final product.

effects, including anti-oxidant, anti-cancer, HIV reverse transcriptase inhibition, neuroprotective, anti-fungal, anti-bacterial, and anti-diabetic properties [15]. Isatin is a viable tail scaffold for creating compounds with promising carbonic anhydrase inhibitory activity profiles against tumor-associated CA isoforms IX and XII [16-17]. Depending on this background benzene sulfonamide as a zinc anchoring moiety linked to an isatin tail through ethyl p-aminobenzoate were created and combined to function as CAIs.

AIM

To evaluate compound I, II, III, and IV's anticancer properties that have just been produced. These substances were created with the specific purpose of targeting solid tumors' carbonic anhydrase enzyme.

MATERIALS AND METHODS

CHEMICAL SYNTHESIS

The following scheme explains the design of a new compounds pathway for it compounds derived from sulfonamide

THE SOFTWARE AND SYSTEM OF THE COMPUTER

We utilize Chem Draw professional Software Pro 12.0 and Molecular Operating Environment (MOE) 2015 both of which is downloaded.

LIGAND AND RECEPTOR PREPARATION WITH MOLECULAR DOCKING PROCEDURE

Chem Draw Professional (12.0) was used to precisely draw the ligand molecular structures. Following that, the ligand is protonated in a three-dimensional shape, partial charge is added, energy is minimized, and the results are saved. We extract the receptor from (MOE), which is the crystal structure of genetically altered CA XII (PDB: 1JCZ /chain A).

The following steps are used to prepare the target protein:

The remaining chain sequences were removed, leaving only the ones implicated in the protein function. The minor molecules were eliminated. Additionally, molecules of water were eliminated. Fixing the potential of the protein atoms and determining its active site comes first, as adding hydrogen conceals bonds.

Table 1. Binding properties of newly synthesized compounds with CA XII (PDB: 1JCZ/ chain A)

Compound	Docking S- scores in ΔG (Kcal/mol)	RMSD	Number of binding sites	Molecules that involve in binding
ACTAZOLAMIDE	-5.82	2.094	3	Zn 3:901, Thr199, Lys67
I	-6.64	1.321	4	Zn 3:901, Thr199, His96, His94
II	-6.89	1.678	5	Zn 3:901, Thr199, His96, His94, Ser132
III	-7.12	1.921	6	Zn 3:901, Thr199, His119, His96, Ser132, Leu198
IV	-6.75	1.211	7	Zn 3:901, Thr200, Thr199, His94, Lys67, Ser132, Leu198

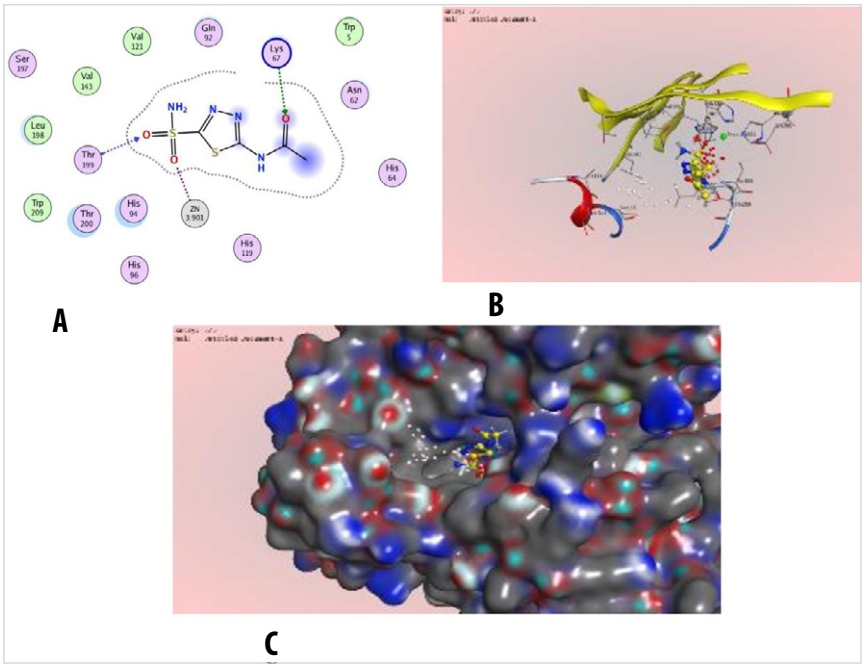

Fig. 1. Acetazolamide with Carbonic anhydrase XII (PDB code: 1JCZ), where (A) explain the 2D picture of binding Acetazolamide with active site, (B) explain the 3D picture of binding Acetazolamide with an active site and (C) explains the 3D picture of entrance and binding with whole protein.

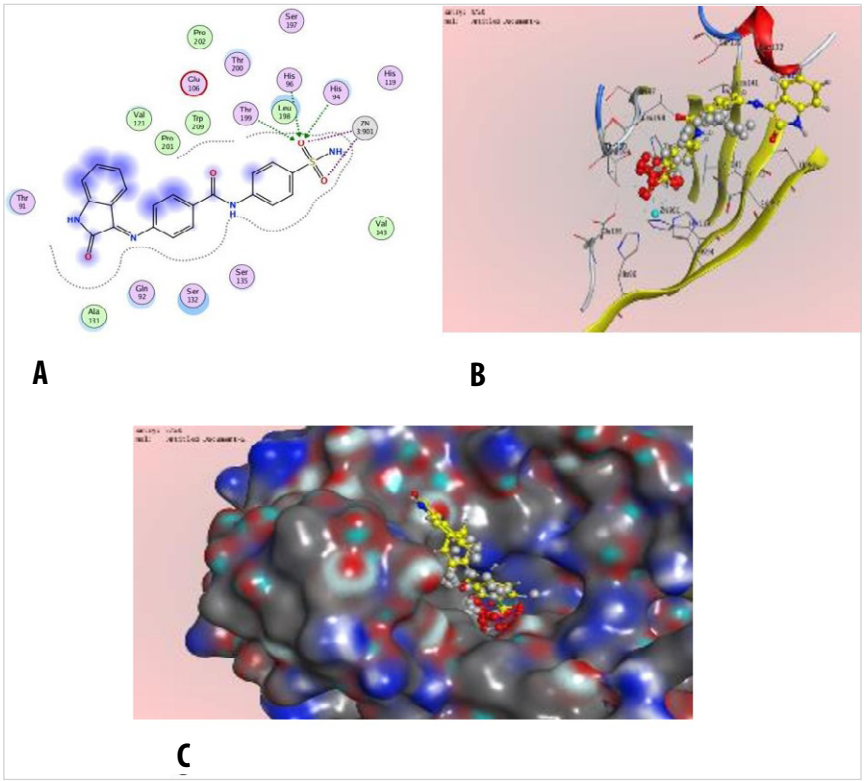

Fig.2. Compound I with Carbonic anhydrase XII (PDB code: 1JCZ), where (A) explain the 2D picture of binding Compound I with active site, (B) explain the 3D picture of binding Compound I with an active site and (C) explains the 3D picture of entrance and binding with whole protein.

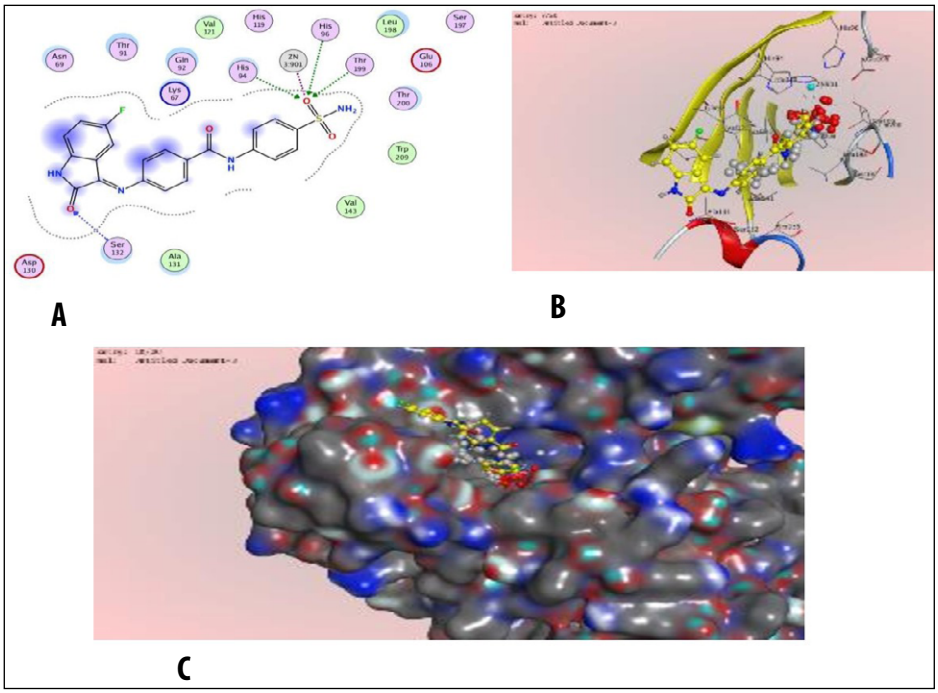

Fig. 3. Compound II with Carbonic anhydrase XII (PDB code: 1JCZ), where (A) explain the 2D picture of binding Compound II with active site, (B) explain the 3D picture of binding Compound II with an active site and (C) explains the 3D picture of entrance and binding with whole protein.

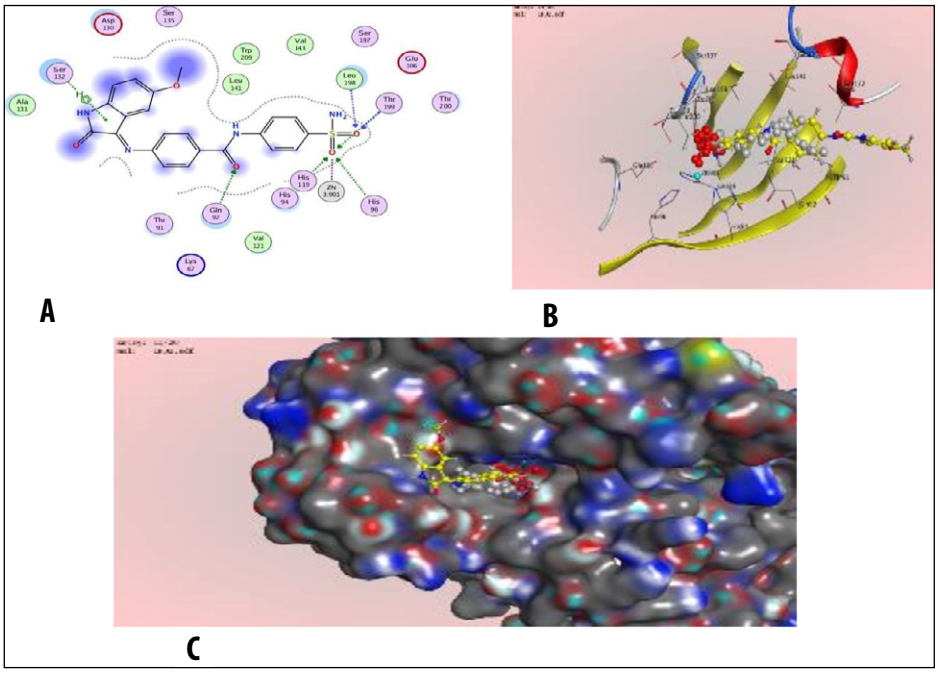

Fig.4. Compound III with Carbonic anhydrase XII (PDB code: 1JCZ), where (A) explain the 2D picture of binding Compound III with active site, (B) explain the 3D picture of binding Compound III with an active site and (C) explains the 3D picture of entrance and binding with whole protein.

The final step involves loading the previously generated ligand from saved data into MOE and starting the docking process [18].

RESULTS

MOLECULAR DOCKING AND VIRTUAL SCREENING

The goal of molecular docking is to use computer-based techniques to prepare for the ligand-receptor complex [19]. The software also offers capabilities for comparing the binding modes of several ligands to the same protein target and for displaying and analyzing the docking data [20]. Molecular Operating Environment (MOE) explains binding specificity of new synthesized compounds to carbonic anhydrase XII enzyme in the same manner as the active site of acetazolamide. The developed compounds' inhibitory actions were graded depending on the value of S. Score and Rmsd (Root mean square deviation), which is showing distance average between the atoms of the pose and original ligand for the site of the anti-cancer that studied, and the similarity in amino acids that entering in the inter-

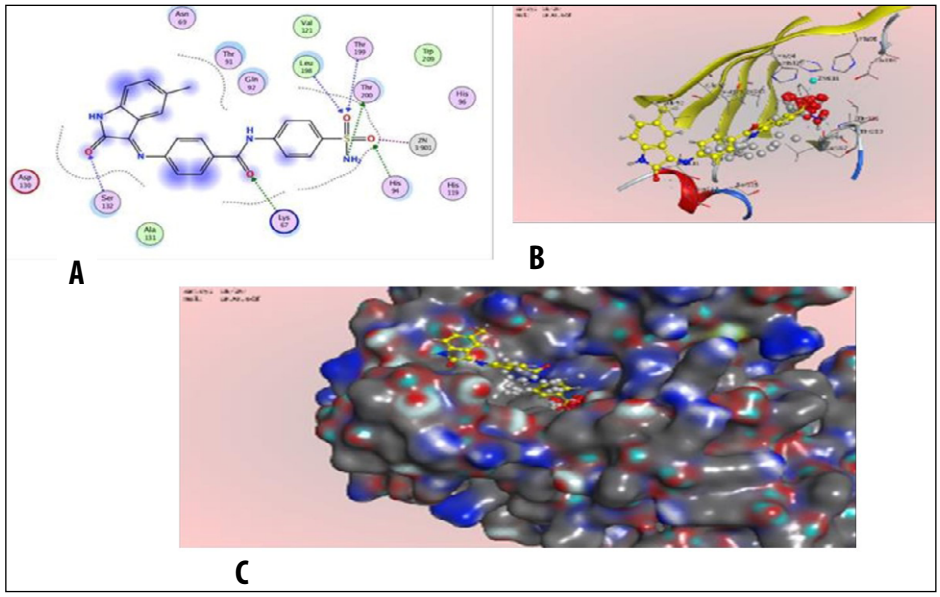

Fig.5. Compound IV with Carbonic anhydrase XII (PDB code: 1JCZ), where (A) explain the 2D picture of binding Compound IV with active site, (B) explain the 3D picture of binding Compound IV with an active site and (C) explains the 3D picture of entrance and binding with whole protein.

action on the same active site. Interaction between acetazolamide and its interaction site, consisting of Zn 3:901, Thr199, and Lys67 (Table 1).

DISCUSSION

The compounds' effectiveness as anticancer drugs against the carbonic anhydrase XII enzyme were assessed by the Molecular Operating Environment docking results; most of the compounds that were examined had good binding affinity with target proteins in comparison to acetazolamide. With the highest s. score (–7.12), compound III demonstrates how the methoxy substitution improves the orientation of the proposed ligand in the receptor pocket. In comparison to other molecules, the compound IV with methyl substitution created more hydrogen bonds with a number of significant amino acid residues in the protein, giving it a more stable orientation and a stronger binding affinity. Compound II with a fluoro substituent exhibits a high S. score (–7.46) and good rmsd. On the other hand, the inhibitor lacking substitution exhibits a reduced s. score (–6.64) and a low Rmsd (1.321).

CONCLUSIONS

This work aims to quantify and enhance the in-Silico interaction between sulfonamide derivative chemicals and the carbonic anhydrase enzyme. To evaluate the effectiveness of newly synthesized compounds as carbonic anhydrase XII inhibitors, use the Molecular Operating Environment (MOE). When compared to acetazolamide, most of the compounds revealed an enhanced binding affinity with the target proteins. All compound has greatest S. score especially compound III had the greatest S. Score (-7.12), suggesting that the methoxy alteration improves the recommended ligand's orientation within the receptor pocket. This displayed the substitution of isatin improves binding interaction and improves flexibility binding with carbonic anhydrase XII.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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