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Evaluation of Newly Synthesized Compounds Targeting Carbonic Anhydrase Enzyme for Antineoplastic Activity in Solid Tumors

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Abstract

Objectives: This study was conducted with the aim of assessing the antineoplastic potential of recently developed compounds, namely F3, F4, and F5. These compounds were designed to target the carbonic anhydrase enzyme in solid tumors.

Methods: The synthesis of these compounds involved the utilization of sulfanilamide, chloroacetylchloride, thiourea, benzyl chloride derivatives, and silver nitrate. Docking studies were carried out using the MOE software program version 2015.10, and the cytotoxic activity was predicted through the implementation of the MTT assay.

Results: The compounds that were synthesized displayed noteworthy antineoplastic activity, as evidenced by both in silico simulations and cell line investigations. Notably, Compound F5 exhibited an IC50 value of 9.02 µg/ml for MCF7 cells, signifying a substantial difference when compared to the IC50 value of cisplatin. Moreover, Compounds F3 and F4 exhibited higher S scores in the docking study compared to acetazolamide, implying a more robust binding affinity to the catalytic site of the receptor. The inclusion of a substituted thiazole ring contributed to increased flexibility and enhanced receptor interaction.

Conclusion: The synthetic compounds put forth in this study demonstrated notable antineoplastic properties. Furthermore, the complexation process notably augmented the inhibition of cancer cell growth, underscoring their potential as promising agents for combating cancer.

Keywords: Sulfonamide, thiazole ring, docking study

Introduction

Chemotherapy resistance poses a formidable challenge in the field of cancer treatment, standing as a significant barrier to successful outcomes. Regrettably, it serves as a prime culprit behind the heightened burden of patient suffering and loss of life. Astonishingly, statistics reveal that a staggering ninety percent of cancer patient fatalities can be directly linked to the formidable enemy known as chemotherapy resistance.[1,2] This resistance manifests itself through a myriad of intricate mechanisms: Genetic factors (encompassing gene mutations, amplifications, and epigenetic alterations), augmented DNA repair capacity, heightened metabolism of foreign substances, growth factor signaling ,and enhanced efflux of drugs.[3,4] Thus, it has become imperative to identify a novel therapeutic target that specifically targets the unique properties that differentiate cancer cells from normal cells. One of the defining features of the tumor microenvironment surrounding the mass is the presence of hypoxia, resulting from the heightened oxygen requirements of rapidly proliferating cancer cells.[5] Furthermore, highly proliferative cancer cells exploit oxidative phosphorylation of glucose and anaerobic glycolysis for energy production. This metabolic process generates significant amounts of metabolic acids, necessitating the involvement of various protein complexes to prevent intracellular accumulation of H+ ions and maintain an intracellular alkaline pH.[6] CAs are enzymes located on the cell surface that are upregulated in hypoxic conditions. They belong to the α-CA family of zinc metalloenzymes and are involved in the reversible conversion of CO_2 to bicarbonate ions (HCO_3^-) and protons (H+), through the process of hydration.[7] With regard to human CAs (hCAs), 15 CA isozymes emerging from the α-family have been characterized. These isoforms differ in terms of their catalytic activity, protein structure, cellular localization, and response to various types of modulators.[8] hCA IX and XII are predominantly present in hypoxic cancers and contribute significantly to the metabolic and pH regulatory machine of tumor cells, supporting their proliferation.[9] Therefore, research has been focused on developing inhibitors targeting this enzyme as a strategy to overcome chemotherapy drug resistance,[10-12] Among inhibitors to CAs the zinc-binding sulfonamides are recognized as a significant class of carbonic anhydrase inhibitors, where their deprotonated form (SO_2NH) coordinates with the zinc cation in the active site of the enzyme. The "tail approach" has come to the forefront as a successful technique for the development of specific isoform inhibitors. In this strategy, the sulfonamide-containing aromatic ring, serving as the zinc-binding group (ZBG), is merged with various tail moieties via functionalized linkers.[13] Moreover, In the realm of medicinal chemistry, the thiazole ring stands as a remarkable scaffold adorned with the exquisite presence of sulfur and nitrogen atoms. This distinctive ring structure has served as a versatile foundation for the design and development of numerous pivotal therapeutic compounds. It is a central part of some clinically used chemotherapies, such as dasatinib, dabrafenib, ixabepilone, patellamide A, and epothilone.[14] In recent times, thiazole-based compounds have been efficiently prepared as potential inhibitors of multiple physiological targets, including cell membrane-associated enzyme-linked receptors, (like polymerase

inhibitors) and the cell cycle (like microtubular inhibitors). Moreover, these compounds have been established to manifest remarkable efficiency, potent tumor-inhibiting activity, and lower toxic effects.[15-17] On the other hand, an intriguing aspect concerning metal complexes of sulfonamide carbonic anhydrase inhibitor is that they act as 10 to 100-fold more powerful inhibitors in comparison to the parent sulfonamide from which they were obtained, it is thought that this potent inhibition is due to a double mode of action, via sulfonamide anions and metallic ions. In dilute solution, the attainment of the desired state is accomplished through the dissociation of the coordination compounds. This approach involves the formation of sulfonamide anions, which subsequently bind to the Zn (II) ion present in the active site of the enzyme. Simultaneously, the metal ions act by obstructing the proton shuttle residues of CA.[18] Based on the aforementioned findings, we have derived a formulation for our novel compounds. Furthermore, the computational study provided validation of the efficacy of these compounds, thereby motivating us to proceed with their chemical synthesis.

Materials and Methods

The chemical reagents and anhydrous solvents used in the experiment were provided by various suppliers, including (Sigma-Aldrich Germany, Reidal Dehean Germany, Hangzhou Hyper Chemicals, and Merck, Germany). The capillary tube technique was used to detect melting points using the Thomas hover apparatus (England). Ascending thin-layer chromatography was used to validate the reaction's stages and the purification of the produced compounds, and to determine the retention factor (Rf) values, with methanol and acetone (1:1) acting as the mobile phases.[19] Shimadzu Japan's spectrophotometer was used by the University of Kufa's College of Pharmacy to scan for FT-IR and estimate spectra using KBr discs. The Mashhad University of medical sciences used the Bruker 300 MHz to record H1NMR data using DMSO as the solvent.

General Procedure

To Sulfanilamide that dissolved in a mixture of benzene: DMF, TEA was added, then the entire mixture was put in an ice bath after that chloroacetyl chloride was dissolved in benzene and added drop by drop to the sulfanilamide mixture. amide group is prepared. The product then reacted with thiourea in ethanol as a solvent to produce a thiazole ring with a primary amine in potion 2 to the thiazole ring. the last primary amine and benzyl chloride derivatives in the presence of TEA were refluxed. The last product was dissolved in ethanol, silver nitrate dissolved also in ethanol was mixed, and a complex form.

Saeedi, M., et al. describe the preparation of 2-Chloro-N-(4-sulfamoylphenyl)acetamide (F1) is made by reacting sulfanilamide with chloroacetylchlorid.[20]

(2 gm, 11.6 mmol) of sulfanilamide dissolved in 40 ml of a mixture of DMF: benzene (1:3), then (1.6 ml:11.6 mmol) of TEA was added. After that, this mixture was stirred in an ice bath, and chloroacetylchlorid (0.92 ml, 11.6 mmol in 10 ml benzene) was added drop by drop to the reaction mixture with continuous stirring this addition take about one hour, followed by reflux for 3 hours. Completion of the reaction was

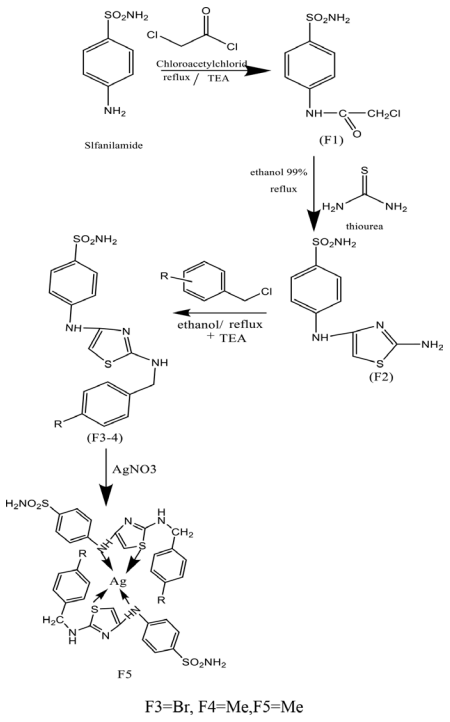

Fig. 1 **Synthesis of final compound and intermediate.**

followed by TLC, then distilled cold water is added, and the precipitated compound was filtered and recrystallized from ethanol.

Jawad, H.A., Synthesis of 4-((2-aminothiazol-4-yl) amino)benenesulfonamide (F2):[21]

(2 mmol, 0.53 gm) of compound (F1) was dissolved in 50 ml absolute ethanol and (2 mmol, 0.16 gm) of thiourea is added the reaction mixture is refluxed for 10 hours, and the solvent is evaporated and recrystallized by ether. Then HCl was removed.

Synthesis of 4-((2-((4-bromobenzyl)amino) thiazol-4-yl)amino) benzenesulfonamide (F3) according to Park, H.-S., et al. with some modifications:[22]

2 mmol of compound F2 dissolved in a mixture of ethanol: DMF (1:1) and put in the ice bath, then 2 mmol of TEA is added, then 4-bromo benzyl chloride is also dissolved in mixture of ethanol: DMF after that it was added to compound F2 slowly drop by drop then reflexed for 8 hour, at the end of reflex hours solvent was evaporated, the product then dissolved in ethyl acetate, washed in distill water, and filtered over magnesium sulfate, the filtrate was evaporated to give compound F4, that recrystallized from ethanol.

Synthesis of 4-((2-((4-methylbenzyl)amino) thiazol-4-yl) amino) benzenesulfonamide (F4):[22] 2 mmol of compound F2 dissolved in a mixture of ethanol: DMF (1:1) and put in the ice bath, then 2 mmol of TEA is added, then 4-methyl benzyl chloride is also dissolved in mixture of ethanol: DMF after that it was added to compound F2 slowly drop by drop then reflexed for 8 hour, at the end of reflex hours solvent was evaporated, the product then dissolved in ethyl acetate, washed in distill water, and filtered over magnesium sulfate, the filtrate was evaporated to give compound F4, that recrystallized from ethanol.

Preparation of complex (F5) 2 mmol of compound F4dissolved in 99% ethanol, then 2 mmol of silver nitrate is dissolved in 99% ethanol, the two mixtures were mixed and

refluxed for one-hour, the final mixture was concentrated by drying the solvent and the precipitate was washed with ethanol and allow to dry.[2]

Physical Properties

Sulfanilamide ($C_6H_8N_2O_2S$), white crystal, Mw = 172.2 g/mol, melting point = 165°C

Compound F1 $C_8H_9ClN_2O_3S$, gray powder, Mw = 248.7 g/mol, melting point = 197°C, Rf value = 0.72, % yield = 90%

Compound F2 $C_9H_{10}N_4O_2S_2$, apricot color powder, Mw = 270.3 g/mol, melting point = 105°C, Rf value = 0.75, % yield = 86%

Compound F3 $C_{16}H_{15}BrN_4O_2S_2$, light yellow powder, Mw = 439.3 g/mol, melting point = 153°C, Rf value = 0.69, % yield = 90%

Compound F4 $C_{17}H_{18}N_4O_2S_2$, orange powder, Mw = 374.5 g/mol, melting point = 137°C, RF value = 0.71, yield = 90%

Compound F5 silver complex, beji powder, Mw = 856.8 g/mol, melting point = 225°C

Spectroscopic Analysis

Compound F1 $C_8H_9ClN_2O_3S$ IR (cm^{-1}) 3475 N-H primary sulfonamide, (3373-3331) N-H_2 primary amine, 1689 C=O amide, 1602-1546 C=C of aromatic ring 678 C-Cl.

Compound F2 $C_9H_{10}N_4O_2S_2$ IR (cm^{-1}) 3475 N-H OF primary sulfonamide, (3373-3331) N-H_2 primary amine, 1629 C=N stretching vibration of thiazole ring, 1600, 1510 C=C of an aromatic ring ^{1}H NMR (ppm): 6.9 singlet ^{1}H of sulfonamide, 7.8 multiplate, 4H benzene ring, 8.8 singlet 1H of secondary amine, 7.1 singlet, ^{1}H of thiazole ring and 6.9 singlet 2H of primary amine.

Compound F3 $C_{16}H_{15}BrN_4O_2S_2$ IR (cm^{-1}) 3321, 3213 NH_2 stretching vibration of primary amine, 2985 C-H stretching vibration of an aromatic ring, 2682 C-H stretching vibration aliphatic, 1633 C=N stretching vibration of thiazole ring, 1516 C=C stretching vibration of aromatic ring. 686 Br-C stretching vibration. ^{1}H NMR (ppm) 6.92 singlet, 2H of sulfonamide, 6.91 triplet ^{1}H of secondary amine that attached to position 2 of thiazole ring, 7.57 singlet, ^{1}H of secondary amine that attached to position 5 of thiazole ring, 7.55, 7.4, 7.3, 7.2, 7.1 Multiplate, 9H signals result from overlapping of non-equivalent aromatic protons, and 4.34 doublet, 2H of CH_2.

Compound F4 $C_{17}H_{18}N_4O_2S_2$ IR (cm^{-1}) 3325, 3209 NH_2 stretching vibration of primary amine, 2976 C-H stretching vibration of an aromatic ring, 2742, 2677 C-H stretching vibration aliphatic, 1633 C=N stretching vibration of thiazole ring. ^{1}H NMR (ppm) 6.92 singlet, 2H of sulfonamide, 6.91 triplet ^{1}H of secondary amine that attached to position 2 of thiazole ring, 7.57 singlet, ^{1}H of secondary amine that attached to position 5 of thiazole ring, 7.55, 7.4, 7.3, 7.2, 7.1 multiplate, 9H signals result from overlapping of non-equivalent aromatic protons, and 4.34 doublet, 2H of CH_2. 3.9 Singlet 3H of CH_3

Compound F5 FTIR chart change and shift in the position of the peak was an indication for complex formation also change in physical properties and melting point suggest compound formation.

Docking Study

The study involved utilizing the 2015.10 version of the MOE (Molecular Operating Environment) software to conduct a molecular docking analysis, which encompassed the preparation of both the protein and ligand structures. The ligand was prepared within the MOE software by performing tasks such as protonation of a three-dimensional structure, addition of partial charges, and energy minimization. The protein with the identifier 4z0q was sourced from the PDB website (www.rcsb.org) and underwent processing steps, including the removal of solvent molecules and non-essential components, specifically targeting the carbonic anhydrase IX for enhanced interaction with ligands. Protons that were originally absent (to facilitate the protein's transfer to and from PDB) were reintroduced, and any broken bonds were repaired while assessing the protein molecule's potential. The active site of the carbonic anhydrase was designated using the MOE software, and the amino acids comprising the site were subsequently identified.

Cytotoxic Study

The MCF7 cell line, representing a type of human breast cancer cells, and the MCF10A cells, which are non-malignant breast epithelial cells, were obtained from the Pasteur Institute's National Cell Bank of Iran. These cells were cultivated using two distinct media types: RPMI-1640 and DMEM, each supplemented with 10% FBS and antibiotics (penicillin at a concentration of 100 U/mL and streptomycin at a concentration of 100 µg/mL). The cells were maintained in a controlled environment with a temperature of 37°C, 5% CO_2, and adequate humidity. To passage the cells, trypsin/EDTA and phosphate-buffered saline (PBS) solution were utilized. The same culture conditions and media were employed for growing 3D colonies as in the standard monolayer cell culture. To evaluate cell growth and viability, the MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium Bromide) assay was employed. For the monolayer cell culture, cells were detached using trypsin, counted, and seeded into 96-well plates at a density of 1.4×10^4 cells/well in 200 µl of fresh medium. Once a monolayer was formed, the cells were exposed to various concentrations of compounds (ranging from 100 µg/mL to 6.25 µg/mL) for 24 hours at 37°C with 5% CO_2. Following treatment, the supernatant was removed, and the cells were incubated with an MTT solution (0.5 mg/mL in PBS) for an additional 4 hours at 37°C. Afterward, the supernatant was replaced with dimethyl sulfoxide (100 µL per well), and the cells were incubated on a shaker at 37°C until complete dissolution of the crystals. The absorbance at 570 nm was measured using an ELISA reader to determine cell viability. The IC50, which represents the concentration of compounds resulting in 50% cell death, was calculated based on the corresponding dose-response curves.

Result and Discussion

The nucleophilic attack of electron pairs on the nitrogen atom in the primary amine of sulfanilamide towards chloroacetyl chloride and the synthesis of 2-chloroacetamide derivative is evident from the presence of a distinct sharp band at 1689 cm^{-1}. The enhanced nucleophilic reactivity towards acid chlorides results in selectivity at the α-carbon atom of chloroacetyl chloride. This selectivity can be attributed to differences in electrophilicity between the two carbon atoms within chloroacetyl chloride. Additionally, electronic and steric factors contribute to the overall selection process.[21]

The synthesis of the thiazole ring involves the reaction of 2-chloroacetamide with thiourea. The presence of a hydrogen bond with the carbonyl oxygen of the acetyl chloride enhances the electrophilicity of this group, facilitating the formation of a thiazole ring through the attack of the amino nitrogen of thiourea and the sulfur of the chloromethyl carbon. Subsequently, the elimination of an HCl molecule occurs. The appearance of a peak at 1629 cm^{-1} confirms the formation of the heterocycle. In the synthesis process of compounds F3 and F4, the aromatic primary amine of the thiazole ring undergoes an N-alkylation reaction with benzyl chloride derivatives. The presence of bands at 2700 cm^{-1} and 2600 cm^{-1}, corresponding to aliphatic C-H bonds, provides evidence for the formation of the intermediate steps. Finally, the change observed in the FT-IR spectrum and the alteration in melting point provides sufficient confirmation of the formation of the silver complex. The results obtained from the FT-IR and 1H NMR spectra strongly support the successful synthesis of the compounds.

Cytotoxic Evalution

The cytotoxic activity of newly synthesized sulfonamide compounds (F3, F4, and F5) was evaluated using cell line MTT assays. These assays provided valuable insights into the effects of the compounds on both cancer cells (MCF7) and normal cells (MCF10a). The IC50 values, representing the concentration required for a 50% reduction in cell viability, were calculated to assess the potency of the compounds. The compounds were compared to two reference compounds, acetazolamide (ACZ) which is the prototype of carbonic anhydrase inhibitor with an antineoplastic effect as new research suggests,[23-25] and cisplatin, which is well-known antineoplastic agent. The dose-response curves, as shown in Figure 2, depict the relationship between the concentration of each compound and its inhibitory effect on MCF7 cell viability.

Figure 2a demonstrates the inhibition activity of acetazolamide, while Figure 2b represents the inhibition activity of cisplatin. Notably, Figures 2c–2e correspond to the inhibition activities of compounds F3, F4, and F5 respectively.

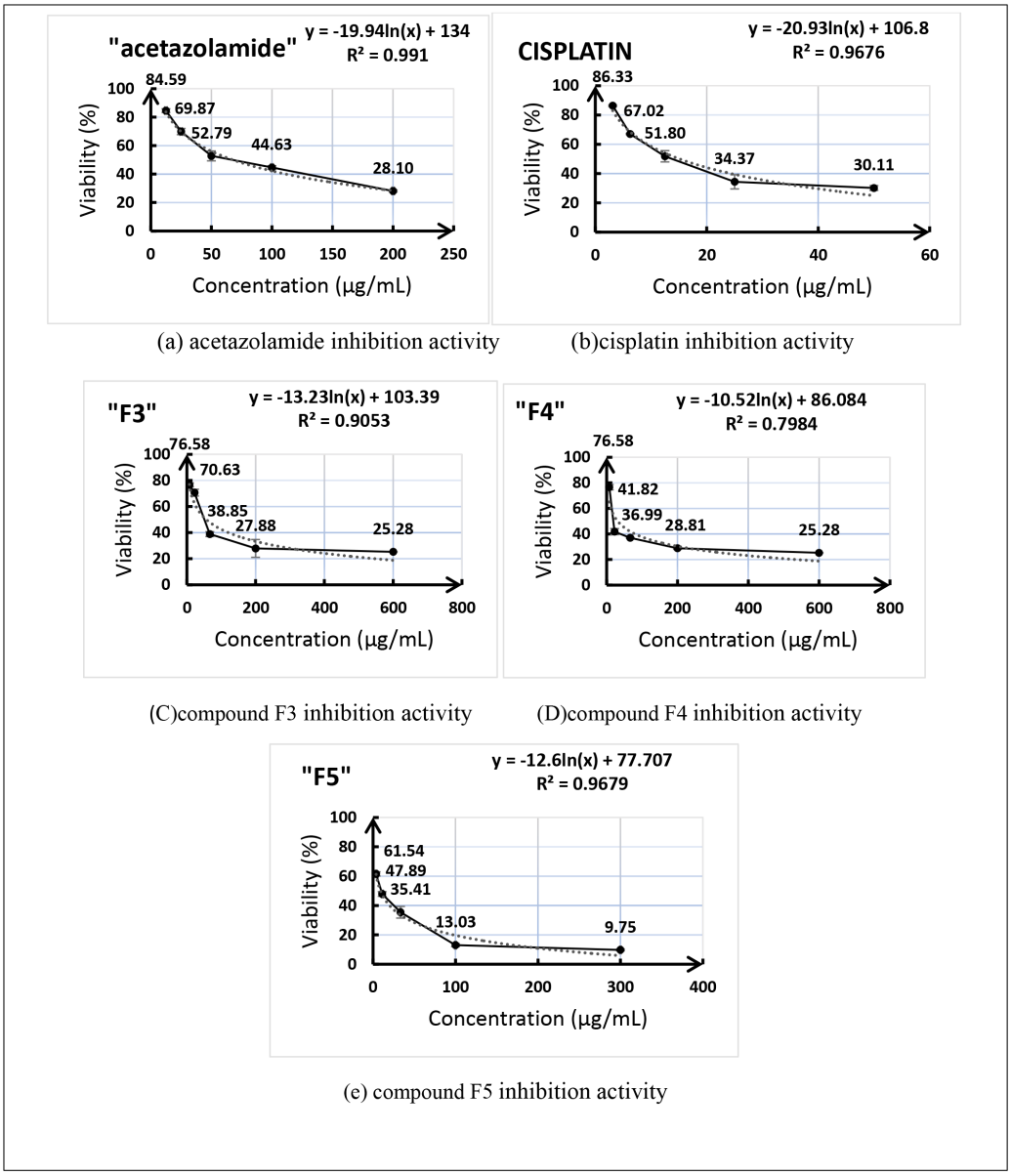

Fig. 2 **Cytotoxicity analysis: unveiling the effects of standards and final compound on MCF7.**

Figure 3 display the relationship between concentration and effect by plotting the viability data of MCF10a cells against the corresponding concentrations of the compounds. The curves depicted the suppressive effects of multiple compounds namely acetazolamide (Figure 3a), cisplatin (Figure 3b), compound F3 (Figure 3c), compound F4 (Figure 3d), and compound F5 (Figure 3e). Each curve represented the response of MCF10a cells to increasing concentrations of the respective compound, highlighting the inhibitory effects on cell viability.

The computation of the IC50 values has been conducted based on the provided dataset. An assessment of the impact of Acetazolamide, cisplatin, F3, F4, and F5 on MCF7 and MCF10a cell lines has been undertaken to elucidate their anti-neoplastic characteristics, and the results are summarized in Table 1. In the context of synthesized compounds, it is discerned that F3, characterized by the presence of a bromine substituent (R=Br), exhibits a moderate level of cytotoxicity, with IC50 values of 56.57 µg/ml for MCF7 and 63.91 µg/ml for MCF10a. This observation suggests that the bromine substituent may be a contributory factor to its antineoplastic activity, albeit to a slightly lesser extent when juxtaposed with the standard compounds.

The nuanced evaluation of the synthesized compounds, namely F3, F4, and F5, has unveiled disparate degrees of cytotoxicity. Particularly, F3, possessing a bromine substituent (R=Br), manifests noteworthy cytotoxicity characteristics, which are underscored by its IC50 values of 56.57 µg/ml for MCF7 and 63.91 µg/ml for MCF10a. This observation serves to highlight the potential involvement of the bromine substituent in augmenting the antineoplastic properties of F3, though to a marginally lesser extent in comparison to the established reference compounds. These findings underscore the significance of unraveling the structure-activity relationships inherent in these compounds for potential therapeutic applications, thus constituting a pivotal facet of this scientific inquiry.

While, compound F4, containing R=CH_3, Express IC50 values of 30.88 µg/ml for MCF7 and 148.43 µg/ml for MCF10a. This indicates that compound F4 exhibits selective cytotoxicity towards the MCF7 cell line, making it a promising potential for further investigation as a selective therapy for MCF7-related conditions. However, additional

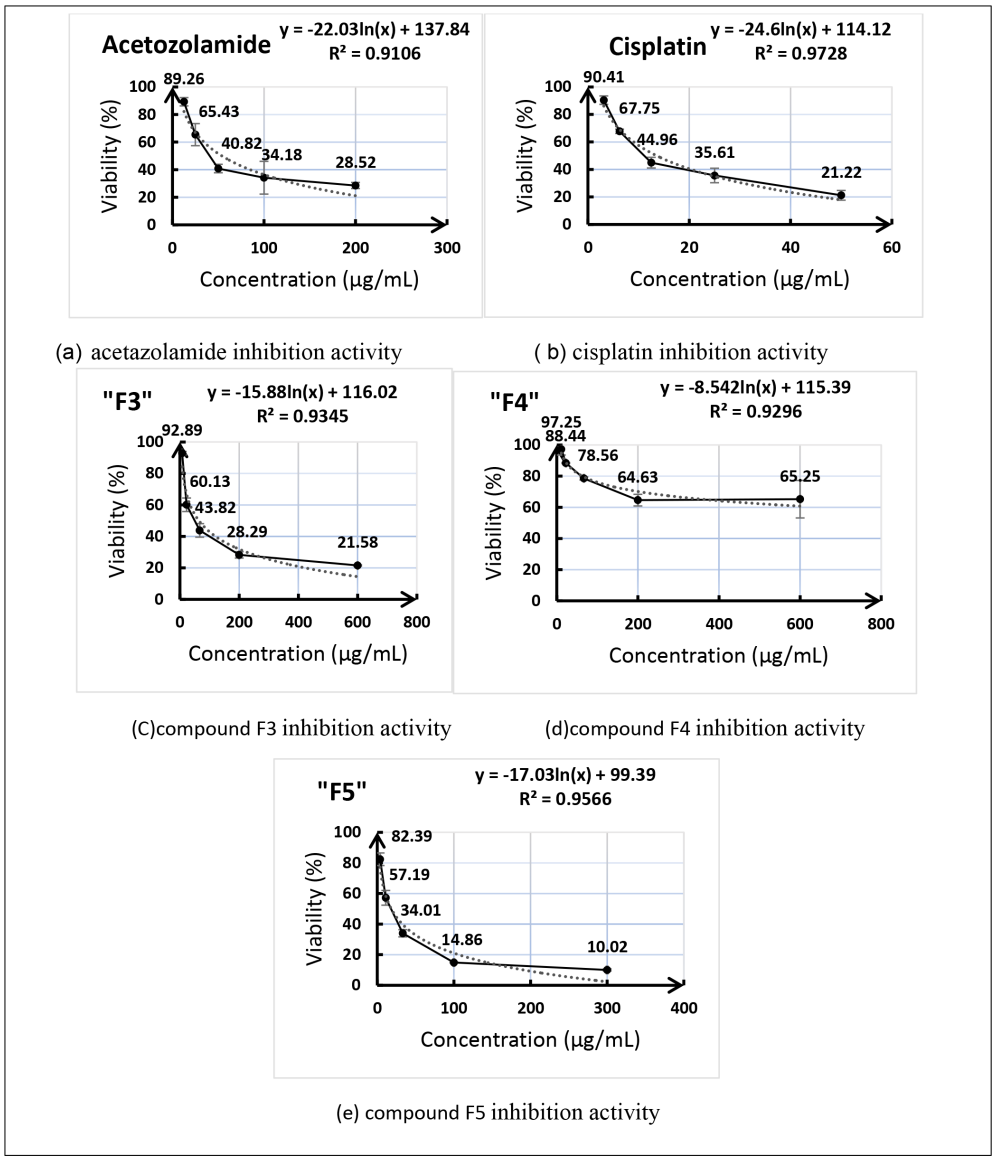

Fig. 3 **Cytotoxicity analysis: unveiling the effects of standards and final compound on MCF10a.**

studies are necessary to illuminate the underlying mechanisms and confirm its potency and safety. Interestingly, compound F5, which includes a silver complex and R=CH_3, show significant cytotoxic effects having an IC50 value of 9.08 µg/ml for MCF7 and 18.18 µg/ml for MCF10a. Incorporating a silver ion into its structure could potentially account for the significant decrease in cell viability, resulting in even lower IC50 values than cisplatin, a well-known chemotherapy agent. Unfortunately, it has lost its selectivity for cancer cells.

Table 1. **The IC50 values of the compounds under investigation were determined, and the data presented represents the average ± standard deviation of three replicate measurements**

Compound	Description	MCF7		MCF10a	
		IC50 (µM) ± SD	*P*-value	IC50 (µM) ± SD	*P*-value
ACZ	Standard	67.53 ± 1.80	Standard	53.91 ± 5.636	Standard
Cisplatin	Standard	15.09 ± 2.25	Standard	13.55 ± 3.45	Standard
F3	Final compound R=Br	56.57 ± 2.58	0.0314 a	63.91 ± 2.42	0.0492 a
			0.0001 b		0.0001 b
F4	Final compound R=CH_3	30.88 ± 1.10	0.0001 a	148.34 ± 4.10	0.0001 a
			0.0001 b		0.0001 b
F5	Final compound with silver complex R=CH_3	9.02 ± 1.70	0.0001 a	18.18 ± 2.45	0.0001 a
			0.0427 b		0.184 n.s

a, b letter's: Significant difference that the comparison with acetazolamide and cisplatin respectively. Ns: non-significant.

Table 2. **Result of docking study**

Compound	Docking-Scores in (ΔG) Kcal/mol	RMSD	Total affinity sites	Molecules that involve in binding
acetazolamide	–5.5846	1.7041	3	Zn1001, Thr A199, Thr A200
F3	–7.043	1.733	3	Zn1001, Thr A199, Thr A200
F4	–7.249	1.317	3	Zn1001, Thr A199, Thr A200

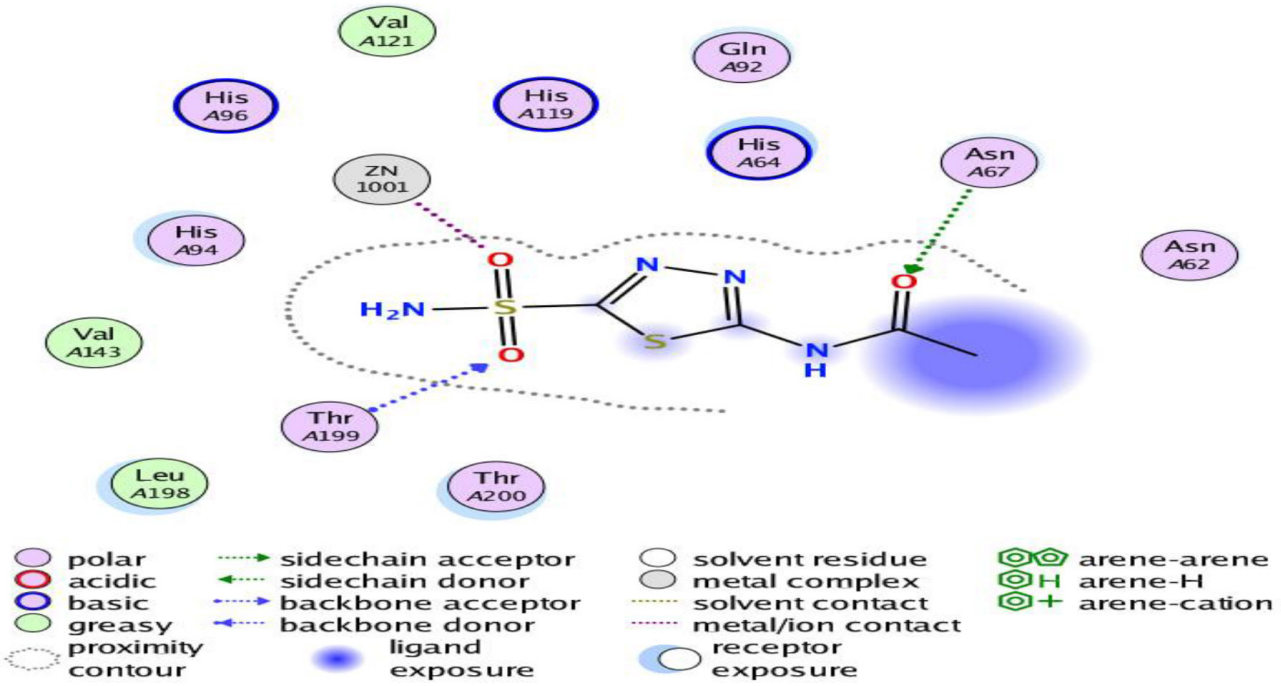

Fig. 4 **A 2D image of acetazolamide interaction with the amino acid residues of the active site of carbonic anhydrase IX protein data bank code 4Z0Q.**

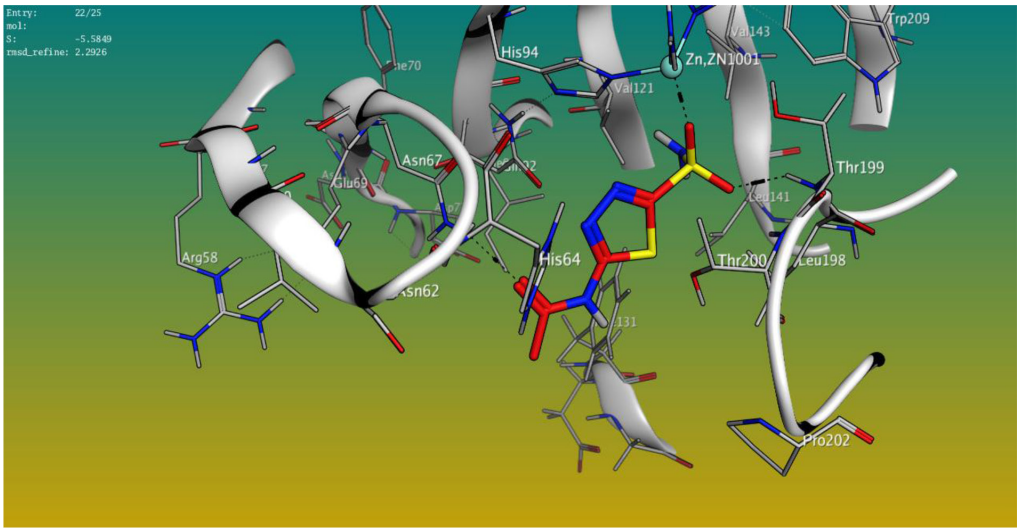

Fig. 5 **A 3D image of acetazolamide interaction with the amino acid residues of the active site of carbonic anhydrase IX protein data bank code 4Z0Q.**

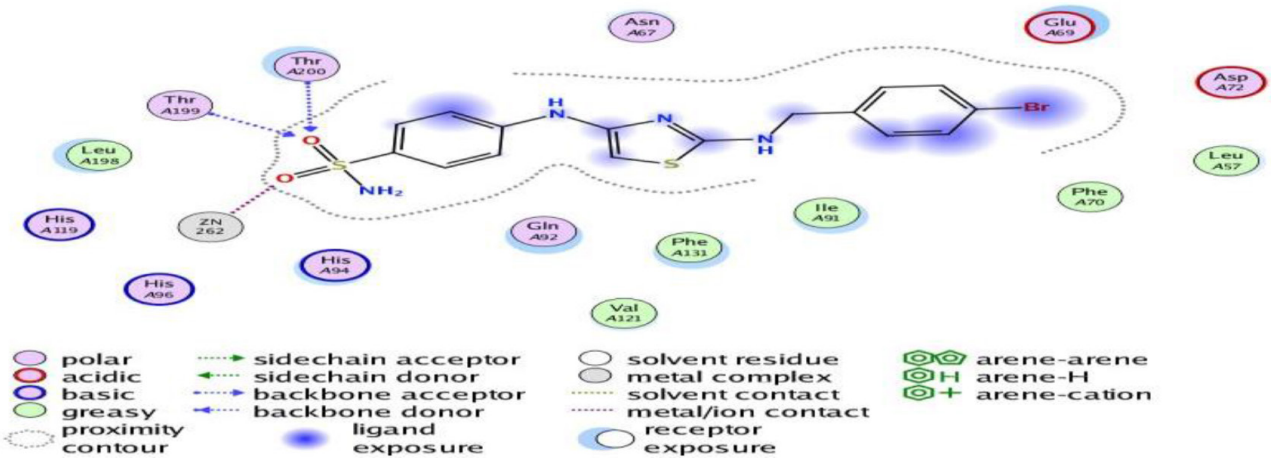

Fig. 6 **A 2D image of F3 interaction with zinc and the amino acid residues of the active site of carbonic anhydrase IX protein data bank code 4Z0Q.**

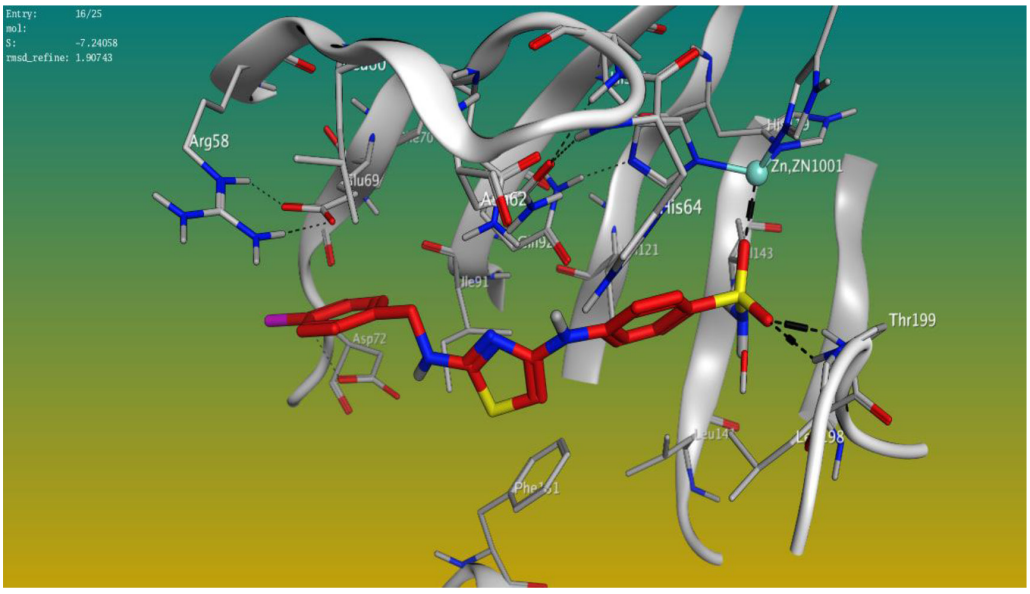

Fig. 7 **A 3D image of F3 interaction with zinc and the amino acid residues of the active site of carbonic anhydrase IX protein data bank code 4Z0Q.**

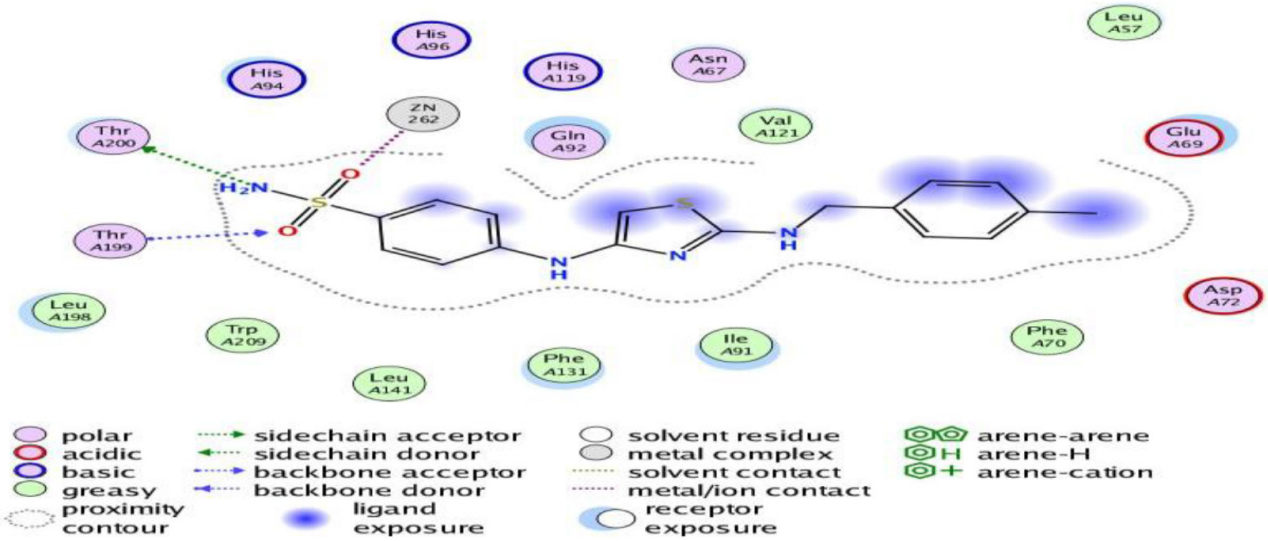

Fig. 8 **A 2D image of F4 interaction with zinc and the amino acid residues of the active site of carbonic anhydrase IX protein data bank code 4Z0Q.**

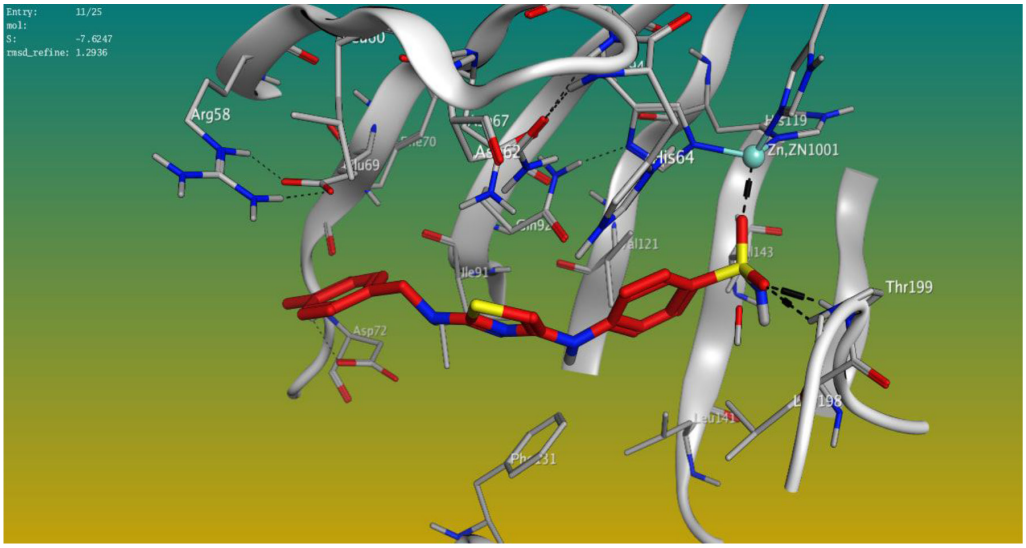

Fig. 9 **A 3D image of F4 interaction with zinc and the amino acid residues of the active site of carbonic anhydrase IX protein data bank code 4Z0Q.**

Docking study

The docking simulations revealed multiple binding modes for the ligands within the binding pocket of the 4Z0Q protein. The binding modes were characterized by the specific residues involved in ligand-protein interactions, including hydrogen bonding, and electrostatic interactions. The results showed a range of binding affinities among the prepared compound, exhibiting stronger interactions with the target protein than acetazolamide. It was observed that synthesized compounds have somehow similar inhibition activity both of them interact with zinc ions which is crucial for inhibition activity, and form hydrogen bound with Th200 and Th199 in the active site of the enzyme. Furthermore, the existence of the thiazole ring appeared to fulfill a crucial role in the binding with the enzyme's catalytic site by promoting the orientation of benzyl derivatives. Consequently, this contributed to the inhibitory activity of these derivatives. The table shows the result of the docking study (Table 2).

Conclusion

In summary, the results of cytotoxic and in silico studies indicate that the synthesized compounds F3 and F4 demonstrate distinct inhibitory effects when compared to the standard compound (acetazolamide) and these differences vary in terms of their statistical significance. Furthermore, F5 (silver complex) exhibits cytotoxic activity against the MCF7 cell line significantly different from the standard cisplatin (known antineoplastic drug). These findings highlight the promising potential of these compounds for further exploration in terms of their possible as anti-neoplastic agents.

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