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Synthesis of Triazole-Imine Derivatives with Antibacterial and Anticancer Potential: An Experimental and in Silico Study

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Keywords: Molecular Docking, Schiff Bases, Triazole Derivatives, Heterocyclic Compounds.

Article History

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Abstract:

This work condensed 4-hydroxybenzaldehyde and triazole-based primary amines to form triazole–imine compounds (A–D). Generated compounds revealed azomethine links in FTIR and NMR. *Streptococcus pneumoniae* and *Bacillus subtilis* antibacterial activity was measured by 0.1, 0.001, and 0.00001 mg/mL agar diffusion derivative C had the largest concentration-dependent inhibition zones of 23 mm against *S. pneumoniae* and 25 mm against *B. subtilis*. MTT also assessed PC-3 and MCF-7 cytotoxicity. The derivative A dose-dependently reduced PC-3 and MCF-7 cell viability by 4.99% and 8%, respectively, at 320 µg/mL. Docking DNA-associated protein (8RZX) explains these biological results. Docking data shows stable binding conformations, with RMSD values around 2 Å and binding energies −2.5 kcal/mol, especially for derivative C. The majority of interactions were hydrogen bonding with phosphate groups and π–π stacking with nucleobases. Experimental and computational evidence suggest triazole–imine compounds are potential antibacterial and anticancer scaffolds.

Keywords: Molecular Docking, Schiff Bases, Triazole Derivatives, Heterocyclic Compounds.

تحضير مشتقات التريازول- إيمين كعوامل واعدة مضادة للبكتيريا والسرطان: دراسة تجريبية وحاسوبية

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الخلاصة:

في هذه الدراسة، تم تكثيف ٤-هيدروكسي بنزالدهيد مع الأمينات الأولية القائمة على التريازول لتكوين مركبات تريازول-إيمين (*A-D*). اظهر طيف الأشعة تحت الحمراءوطيف الرنين النووي المغناطيسي عن وجود روابط أزوميثين في المركبات المُنتجة. تم قياس النشاط المضاد للبكتيريا ضد المكورات الرئوية (*Streptococcus pneumoniae*) والعصوية الرقيقة (*Bacillus subtilis*) باستخدام تراكيز ٠,١ و٠,٠٠١ و٠,٠٠٠٠١ ملغم/مل من مشتق الأجار *C*، حيث أظهر أكبر مناطق تثبيط معتمدة على التركيز، بقطر ٢٣ مم ضد المكورات الرئوية و٢٥ مم ضد العصوية الرقيقة. كما تم تقييم سمية المركبين *PC-3* و*MCF-7* باستخدام اختبار *MTT*. أدى المشتق *A* إلى خفض حيوية خلايا *PC-3* و*MCF-7* بنسبة ٤,٩٩٪ و٨٪ على التوالي، عند تركيز ٣٢٠ ميكروغرام/مل، وذلك بشكل متناسب مع الجرعة. ويُفسر ارتباط البروتين المرتبط بالحمض النووي (*RZX٨*) هذه النتائج البيولوجية. تُظهر بيانات الارتباط تكوينات ارتباط مستقرة، بقيم *RMSD* تقارب ٢ أنغستروم وطاقات ارتباط تبلغ -٢,٥ كيلو كالوري/مول، وخاصةً بالنسبة للمشتق *C*. وكانت غالبية التفاعلات عبارة عن روابط هيدروجينية مع مجموعات الفوسفات وتفاعلات تكديس π-π مع القواعد النيتروجينية. تشير الأدلة التجريبية والحسابية إلى أن مركبات التريازول-إيمين تُعدّ هياكل محتملة مضادة للبكتيريا ومضادة للسرطان.

الكلمات المفتاحية: الالتحام الجزيئي، قواعد شيف، مشتقات التريازول، المركبات الحلقية غير المتجانسة.

1. Introduction:

Heterocyclic compounds play a crucial role in medicinal chemistry due to their diverse biological activities [1]. Synthesis of heterocyclic chemical compounds is an important priority in organic chemical synthesis due to its many uses in health, pharmacology, electronic devices, agricultural production, and other associated domains [2]. Two essential requirements must be addressed by contemporary heterocyclic chemistry methods (reagents, techniques, strategies, reaction processes, chemical and instrumental auxiliaries, catalysts, etc.): "specificity" and "selectivity" (containing common prefixes like chemo, regio, or stereo) [3]. There are two isomers of the triazole ring, a notable five-membered heterocycle containing three nitrogen atoms: The aromatic system 1,2,3-triazole, also known as 1,2,4-triazole, is rich in electrons. Through weak interactions like coordination bonds, hydrogen bonds, ion-dipole interactions, cation stacking, hydrophobic effect, van der Waals force, and so forth, This kind of special

structure enables triazole derivatives to readily bind with a variety of enzymes and receptors in biological systems, leading to a wide range of biological activities[4-6]. Schiff bases, or imines, are essential organic structural motifs. Reversible condensation reactions between a carbonyl molecule and a primary amine generate imines, which have a carbon–nitrogen double bond. Drying agents, molecular sieves, or Dean–Stark traps remove water from the process [7]. Imines are valuable as catalytic ligands, intermediates in the synthesis of nitrogen-containing heterocycles and alkaloids, and players in coordination chemistry. Dantrolene, a muscle relaxant, and thiacetazone, an antituberculosis medication, contain imines [8]. Several organic laboratories have imine synthesis reactions, despite their abundance in biochemical processes in nature. In light of this, a lab study involving imine-based chemical synthesis is crucial[9].

Recent research has focused on triazole-associated Schiff bases with different substituents for antibacterial and anticancer properties. Few studies have linked spectroscopic confirmation, in vitro biological evaluation, and in silico docking against DNA-linked target proteins like PDB ID: 8RZX. Thus, there is little experimental and molecular study on how triazole-imine framework structural variation impacts binding affinity, antibacterial activity, and cytotoxicity.

New triazole-imine molecules are synthesized and tested for biological activity using complementary approaches. The primary research questions: How do triazole amine precursors affect Schiff bases' physicochemical and biological properties? Working with the 8RZX binding pocket, molecular docking may explain antibacterial and anticancer action differences. Answering these questions requires several steps. FTIR and NMR of the target derivative structure following synthesis. Their antibacterial and cytotoxic properties against Gram-positive bacteria and PC-3 and MCF-7 cancer cells are tested. Finally, molecular docking examines binding modes, interaction energies, and structure–activity relationships. Triazole–imine molecules are intriguing bioactive candidates, and this work applies this integrated approach.

2. Materials and Methods:

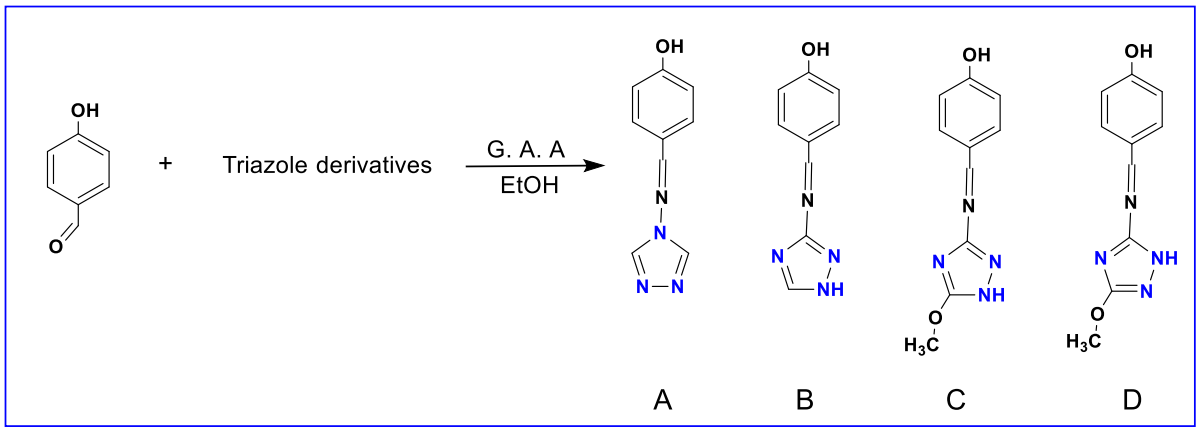
2.1 Material.

Sigma Aldrich provided a variety of amines, including 4-Amino-1,2,4-triazole, 3-Amino-1,2,4-triazole, 3-Amino-5-methylthio-1H-1,2,4-triazole, and 5-Amino-1H-[1,2,4]-triazole-3-carboxylic acid methyl ester. While 100% ethanol, glacial acetic acid, and 4-hydroxybenzaldehyde were acquired from BDH.

2.2 Synthesis of Schiff base derivatives (A-D).

According to Jaafar, M. R., et al (2024) [10], a novel group of imine derivatives (A-D) was synthesized by reacting the same moles of 4-hydroxybenzaldehyde with varying derivatives of triazole that were classified as primary amines. 0.1 mole of 4-hydroxy benzaldehyde dissolved in 20 mL of absolute ethanol and add 2-3 drops of glacial acetic acid; add the amine compound to this solution, and reflux for 3 hours. The mixture is then cooled to room temperature and filtered to collect the precipitate. To synthesize derivative A obtained from 4-amino-1,2,4-triazole; derivative B from 3-Amino-1,2,4-triazole; derivative C from 3-Amino-5-methylthio-1H-1,2,4-triazole; derivative D from 5-Amino-1H-[1,2,4]-triazole-3-carboxylic acid methyl ester, as shown in **Scheme 1**.

The physical properties of synthesized derivative A were obtained as a dark yellow precipitate with a melting point of 187℃. In contrast, derivative B was obtained as a yellow color and (161℃) with a melting point, and derivative C was yellowish-brown and had a melting point of (143℃). Finally, derivative D was formed in a dark yellow color at 181℃.



Scheme 1: Synthesized triazole-imine derivatives (A-D).

2.3 Assessment of Antimicrobial Properties of Schiff-Based Derivatives.

The cup-plate agar diffusion technique evaluates the antibacterial efficacy of derivatives A-C. *Streptococcus pneumoniae* and *Bacillus subtilis* isolated from clinical infections are designated as test organisms. Compounds are formulated in dimethyl sulfoxide at three concentrations: 0.1, 0.001, and 0.00001 mg/mL. Muller-Hinton agar plates are inoculated with bacterial suspensions, and 12 mm wells are filled with test solutions. Ceftriaxone reconstituted in sterile water serves as the reference standard. Following one hour of pre-diffusion, the plates were incubated..." (add what happens next). The antibacterial efficacy of each chemical is evaluated by measuring the inhibition zone diameter in millimeters and comparing it to the reference medicine **[11].**

2.4 The Biotech MTT kit was used to assess several synthetic compounds for cytotoxicity.

Synthesized molecules were evaluated for cytotoxicity against prostate cancer PC3 cells with the MTT assay according to the manufacturer's instructions. MCF-7 cells were seeded at 4.5 × 10^5 per well in sterile 96-well plates containing 200 µL of growth medium. To improve cell adherence, plates were sealed with parafilm, lightly centrifuged, and incubated at 37 °C in 5% CO_2 for 24 hrs. Cells were subjected to a 2-fold serial dilution and treated with synthetic derivatives at concentrations of 0, 20, 40, 80, 160, and 320 µg/mL after incubation. The controlled plate was incubated for 24 hours. Following drug exposure, each well received 10 µL of MTT solution, which was then incubated for 4 hours to allow metabolically active cells to transform MTT into insoluble formazan crystals. After incubation, remove the supernatant and dissolve the formazan in 100 µL of DMSO in each well to preserve the crystals. After five minutes of moderate swirling, the plates melted. 575 nm absorbance was measured using ELISA microplate readers (Bio-Rad, Germany). Cell viability was shown by optical density measurements, and the half-maximal inhibitory concentration (IC_{50}) of the derivatives was ascertained using statistical analysis. This technique assessed cytotoxic effects accurately, consistently, and dependably [12].

2.5 Molecular Docking Process

To investigate the binding mechanism and affinity, the chemically generated triazole–imine compounds (A–C) were docked with the biological target protein (PDB ID: 8RZX) using the Molecular Operating Environment (MOE) tool [13, 14]. Figure 1. Its three-dimensional crystal structure was taken from the Protein Data Bank and generated in MOE by removing crystallographic water molecules and co-crystallized ligands to reduce ligand binding interference. We inserted hydrogen atoms and energy-minimized the protein structure to decrease steric conflicts and maximize form [15]. MOE imported ligand chemical structures drawn in ChemDraw. Ligands were translated into three-dimensional conformationsand geometry was adjusted using a force field to create stable structures. For docking, partial atomic charges and rotatable bonds were assigned for conformational flexibility [16]. The MOE docking simulation active binding area was defined by 8RZX binding pocket nucleotide residues. The placement strategy produced various active site ligand postures. A scoring function calculated the binding free energy. After energy reduction improved top-ranked postures, docking scores, interaction types, and RMSD values were gathered. The research

studied ligand-protein interactions, including hydrogen bonding, π-π stacking, and binding distances.

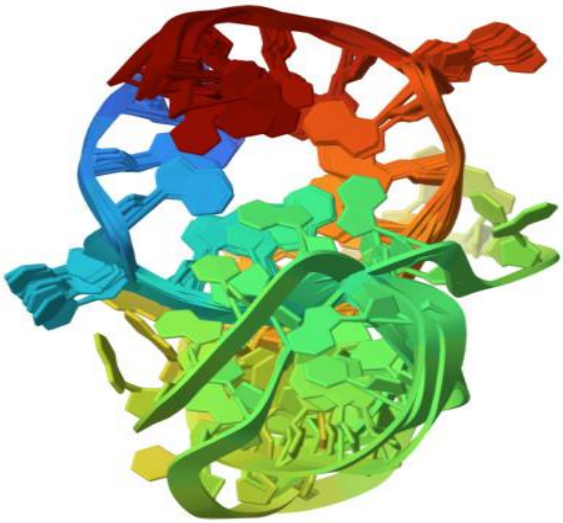


Figure 1: Chemical structure of 8RZX protein.

3. Results and Discussion

The reaction between 4-hydroxybenzaldehyde and different primary amines to produce Schiff base derivatives results in different yellow colors as precipitates. In these reactions, the glacial acetic acid plays a catalytic role to protonate the carbonyl group, and the amine derivative plays a nucleophilic role to attack the carbon of the carbonyl group. In FTIR spectroscopy, the primary amine and the carbonyl group of the aldehyde disappeared and showed a new peak for the imine group **[17, 18]**.

4-(((4H-1,2,4-triazol-4-yl)imino)methyl)phenol (A): The FTIR (cm^{-1}) spectrum shows a peak at 1625 for azo methane group **[19]**, 3336 for the hydroxyl group as a broad band, 3029 for the C-H of the aromatic ring, and 1580 for C=C of the aromatic ring. ^{1}H-NMR (DMSO-d6 as solvent) δ 9.15 (s, 1H, -OH), 8.49 (s, 1H, imine), 7.71 – 7.18 (m, 4H , Ar), as shown in **Figure 2**. ^{13}C-NMR (DMSO-d_6), the key peaks include 155.33 ppm (C-OH), 149.65 ppm (triazole carbon), and 138.87 ppm (ipso-carbon bonded to the linkage). Aromatic methine carbons (CH) appeared at 133.16 and 125.71 ppm, while the ortho-carbons shifted upfield to 114.56 ppm due to the electron-donating effect of the hydroxyl group **[20]**, as shown in **Figure 3.**

4-(((1H-1,2,4-triazol-3-yl)imino)methyl)phenol (B): The FTIR (cm^{-1}) spectrum shows a peak at 1641 for imine group, 3335 for the hydroxyl group, 3055 for the C-H of the aromatic

ring and 1582 for C=C of aromatic ring [21]. ^{1}H NMR (DMSO-d_6) δ 9.91 (s, 1H, -OH), 8.98 (s, 1H, imine), 8.15-7.24 (m, 5H, Ar), as shown in **Figure 4**. ^{13}C NMR (DMSO-d_6) δ 161.01 for aromatic carbon that linked to hydroxyl group, 153.76 for carbon imine group, 149.50-113.81 for aromatic carbon [22], as shown in **Figure 5**.

4-(((5-methoxy-1H-1,2,4-triazol-3-yl)imino)methyl)phenol (C): The FTIR (cm^{-1}) spectrum shows a peak at 1631 for imine group, 3384 for the secondary amine, 3025 for the C-H of the aromatic ring and 1579 for C=C of aromatic ring [21].^{1}H-NMR (DMSO-d_6) δ 9.09 (s, 1H, -OH), 8.67 (s, 1H, imine), 7.75-7.24 (m, 4H, Ar), 5.29 (s, 1H, NH), 3.89 (s, 3H, methoxy)[11], as shown in **Figure 6**. ^{13}C-NMR (50 MHz, DMSO-d_6) δ 162.81 for aromatic carbon that linked to hydroxyl group, 157.70 for carbon triazine ring that linked to oxygen of methoxy group, 152.97 for carbon imine group, 148.02-108.61 for aromatic carbon, 61.26 for methoxy group [23], as shown in **Figure 7**.

4-(((3-methoxy-1H-1,2,4-triazol-5-yl)imino)methyl)phenol (D): The FTIR (cm^{-1}) spectrum shows a peak at 1621 for imine group, 3363 for the secondary amine, 3068 for the C-H of the aromatic ring and 1598 for C=C of aromatic ring.^{1}H NMR (DMSO-d_6) δ 9.01 (s, 1H, -OH), 8.11,(s, 1H, imine), 7.64-7.01 (m, 4H, Ar), 5.26 (s, 1H, NH) [24], 2.98 (s, 3H, methoxy) [10], as shown in **Figure 8**. ^{13}C NMR (DMSO-d_6) δ 162.52 carbon of imine group, 155.49 for carbon triazine ring that linked to oxygen of methoxy group,155.27 aromatic carbon that linked to hydroxyl group, 154.07-122.95 carbons of aromatic group, 59.92 carbon of methoxy group [25], as shown in **Figure 9.**

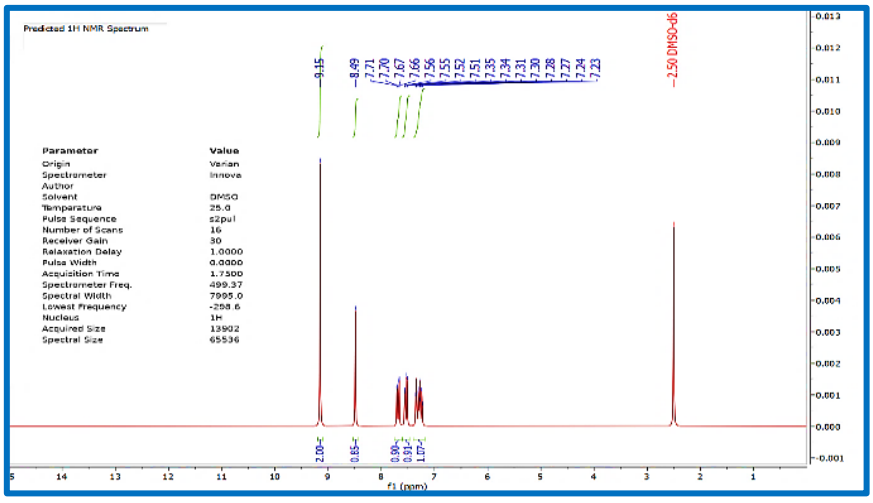


Figure 2: ^{1}H-NMR spectrum of derivative A.

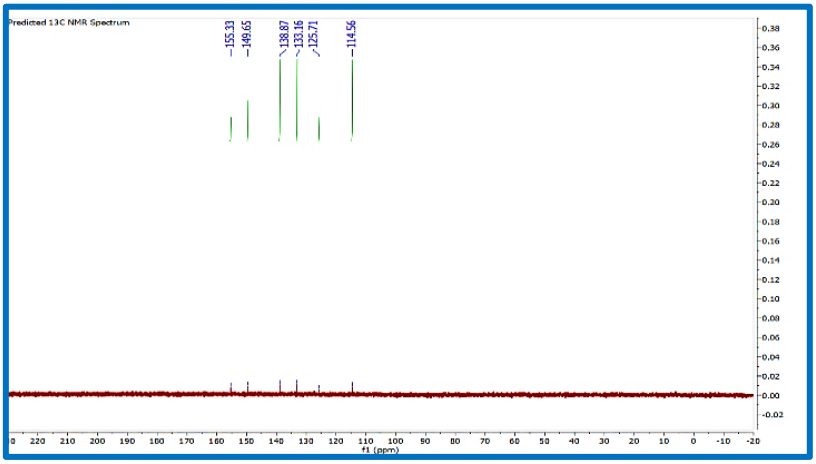


Figure 3: ^{13}C-NMR spectrum of derivative A.

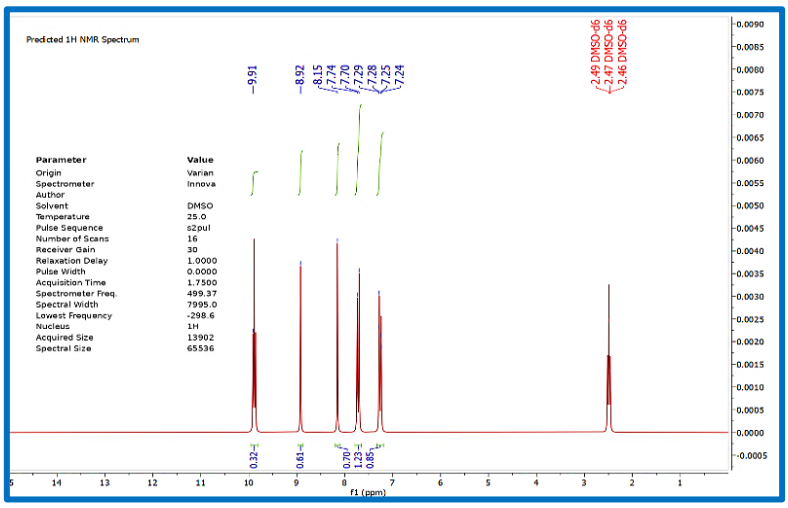


Figure 4: ^{1}H-NMR spectrum of derivative B.

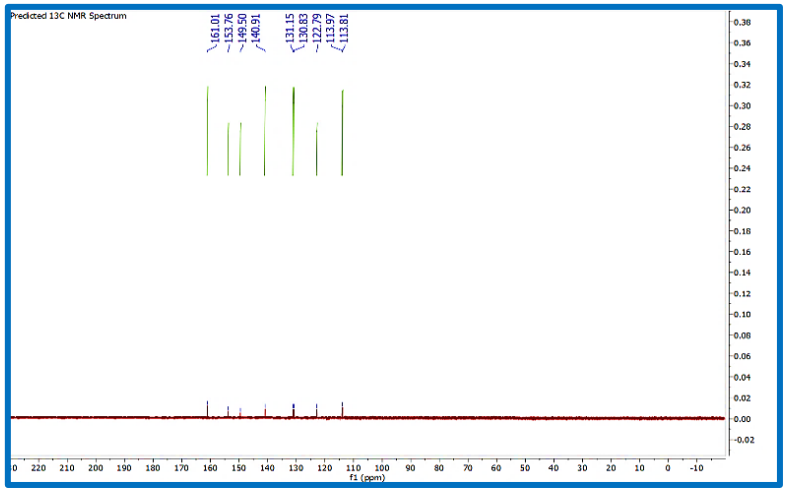


Figure 5: ^{13}C-NMR spectrum of derivative B.

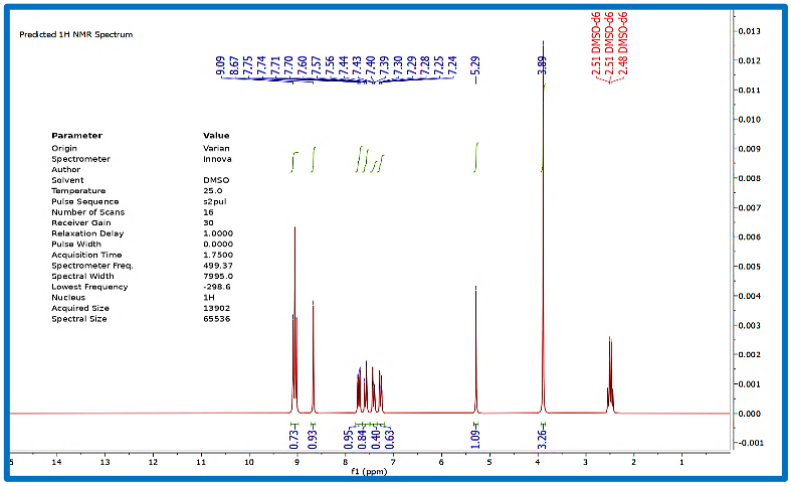


Figure 6: ^{1}H-NMR spectrum of derivative C.

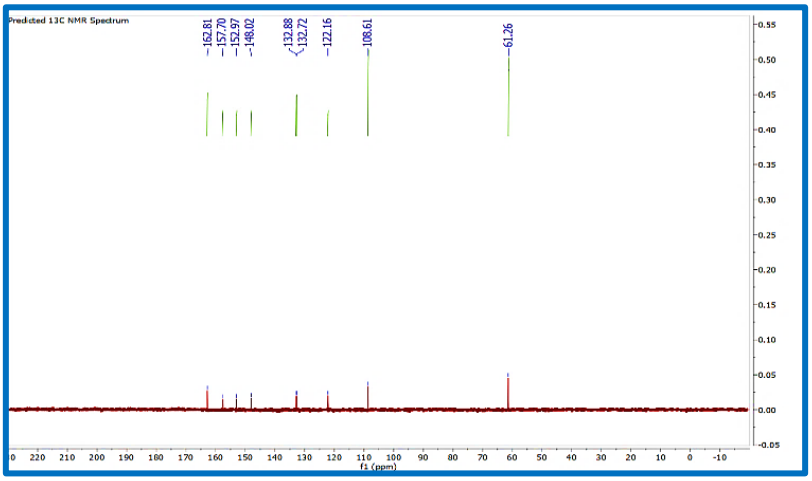


Figure 7: ^{13}C-NMR spectrum of derivative C.

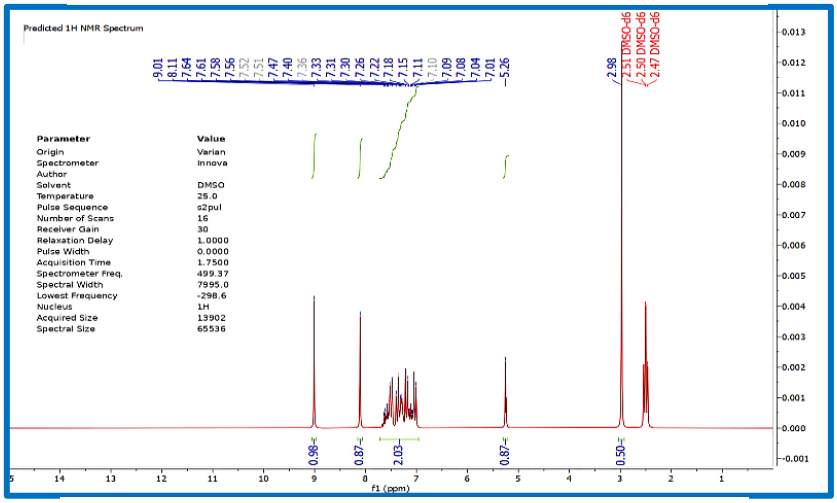


Figure 8: ^{1}H-NMR spectrum of derivative D.

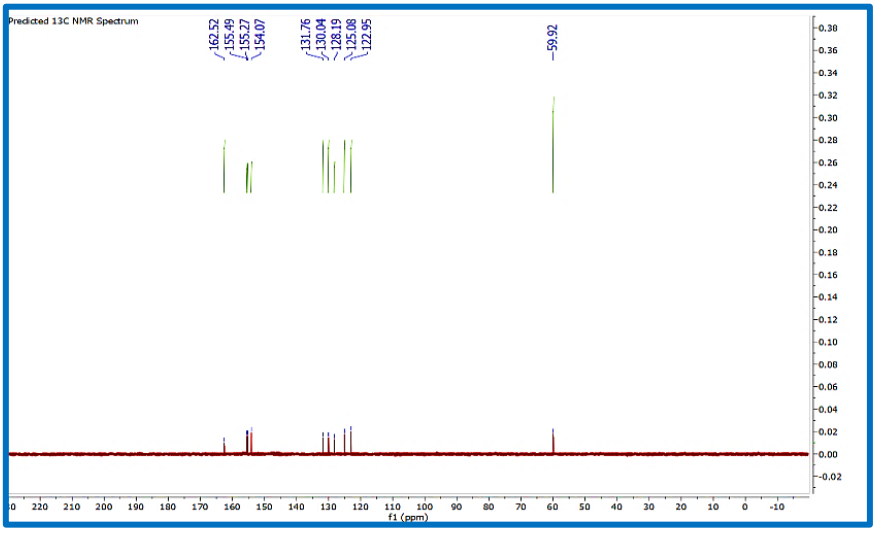


Figure 9: ^{13}C-NMR spectrum of derivative D.

The 8RZX protein has a well-defined binding pocket composed of DNA nucleotides such as DT, DC, DA, and DG. The pocket's mild polarity and aromaticity facilitate the stability of organic ligands by hydrogen bonding with phosphate groups and π–π stacking with nucleobases. The structural characteristics render 8RZX suitable for bioactive ligand evaluation by molecular docking **[26].**

Table 1 describes the physicochemical parameters of the active site of the 8RZX protein. The moderate size of the binding pocket accommodates small aromatic ligands without steric hindrance. Numerous nucleotide residues, particularly DG and DT units, provide a hybrid polar and aromatic milieu. Heteroatom as an aromatic ring ligands bind strongly because of these characteristics. Selective and stable ligand binding and docking interactions of synthetic molecules are made possible by the pocket structure.

Table 1: Binding Pocket Characteristics of 8RZX Protein.

Site	Size	PLB	Hyd	Side	Residues
1	50	2.4	7	51	1:(DT1 DC12 DA13 DG14 DG15 DT16 DG17 DG18 DG19 DC20 DG21)

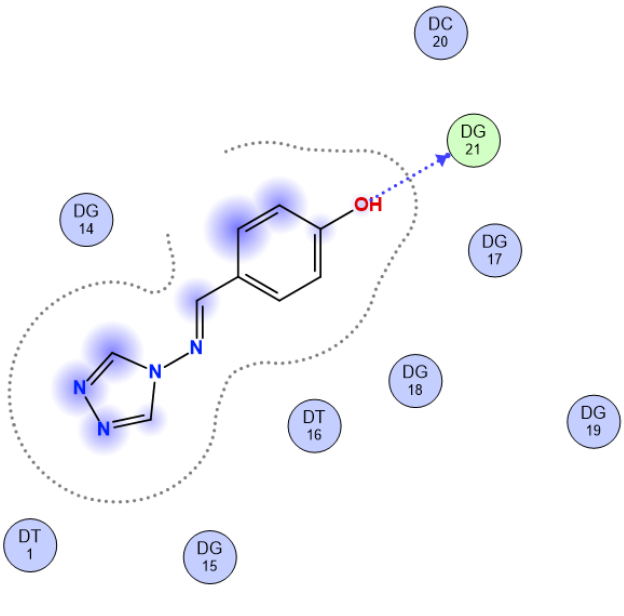
The synthetic 8RZX protein with synthesized derivatives (A-C) together with their docking contacts and binding energies are listed in **Table 2**. The hydrogen bonds that Compound A forms with DG21's OP1 show polar anchoring of the binding site. Compound B's π–π stacking and hydrogen bonding with DG19 and DG21 show enhanced stability via dual contact mechanisms. The most intricate interactions are shown by compound C, which forms π–π stacking with DG21 and hydrogen bonds with DG19. Ligand-protein stability is indicated by moderate binding energies and contact distances. Heteroatoms and aromatic systems boost

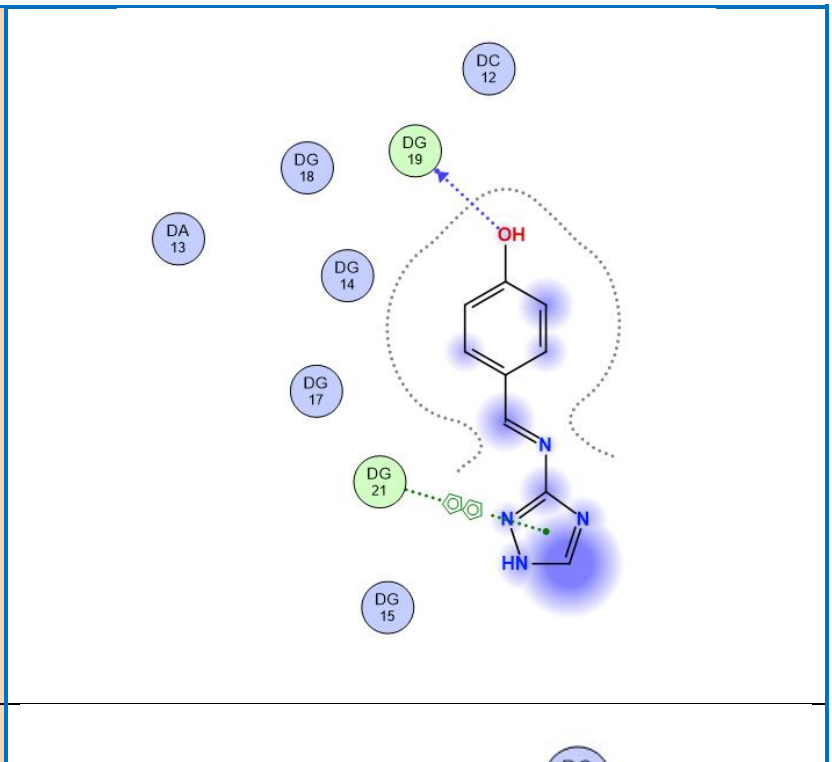
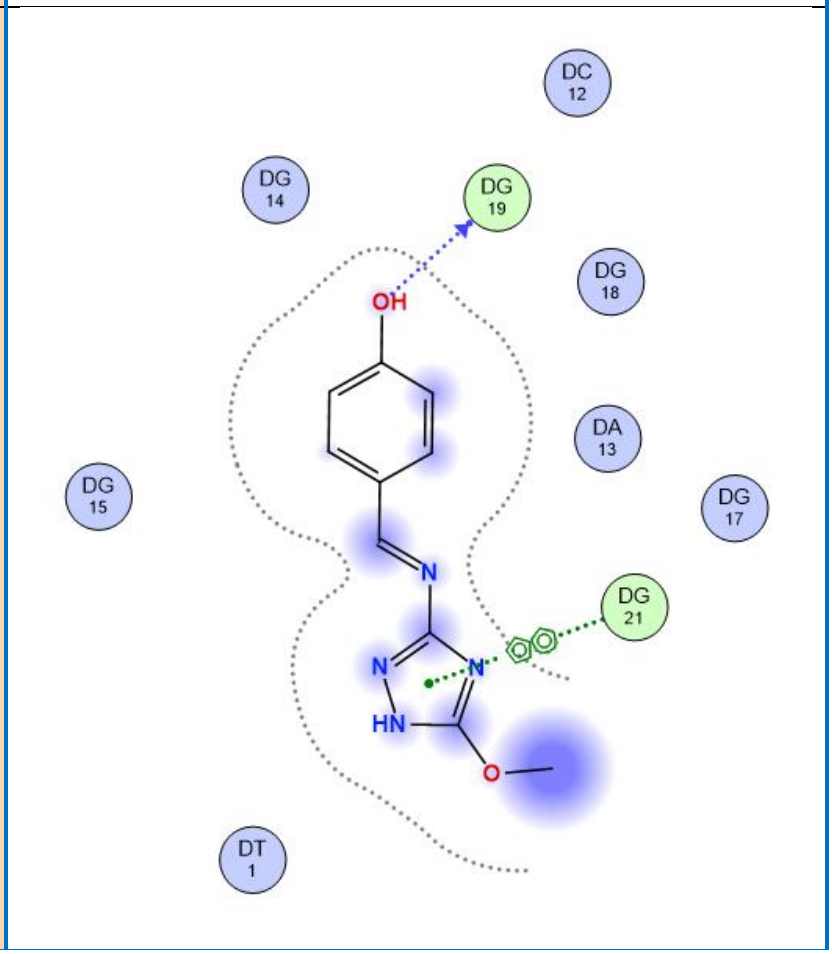
binding affinity, but compound C exhibits superior active site spatial complementarily compared to the others.

Table 2: Docking results for synthesized derivatives interaction with target protein.

Compound No.	Ligand	Receptor	Interaction	Distance (Å)	E (kcal/mol)
A	O 11	OP1 DG 21 (A)	H-donor	3.16	-2.5
B	O 11	OP1 DG 19 (A)	H-donor	2.97	-2.5
	5-ring	5-ring DG 21 (A)	π–π	3.96	
C	O 15	OP1 DG 19 (A)	H-donor	2.92	-2.1
	5-ring	5-ring DG 21 (A)	π–π	3.71	
	5-ring	6-ring DG 21 (A)	π–π	3.60	

Scheme 2 displays the medicines' energy components, RMSD values, and 8RZX receptor docking scores. With RMSD values close to 2 Å, all compounds show stable binding orientations. Compound C has the best docking, indicating stability throughout placement and refinement. Compounds A and B score well after docking and refining. Favorable intermolecular interactions that encourage spontaneous ligand-protein attachment are indicated by negative binding scores. Hydrogen bonding and π–π stacking in compounds are impacted by changes in functional groups and aromatic substitution. Research indicates that modifications to the ligand scaffold significantly influence binding at the 8RZX active site.

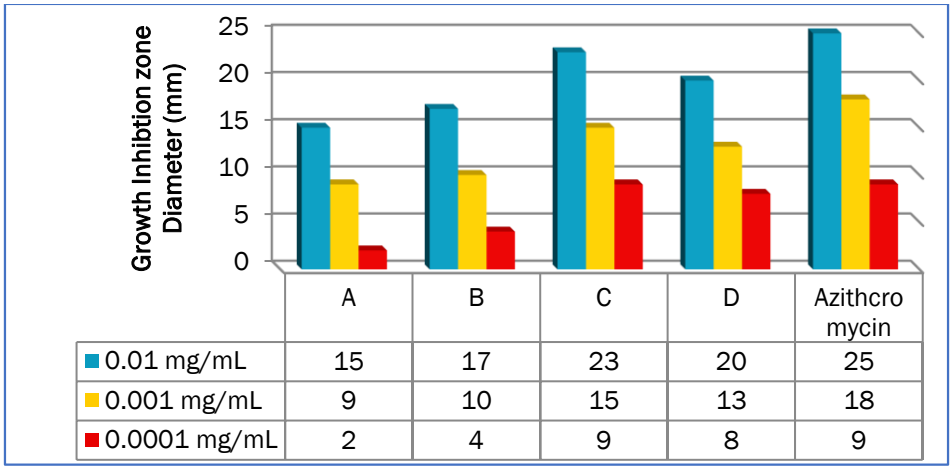
Compound No.	Image
A	

B	
C	

Scheme 2: Interaction details of the synthesized derivatives and the protein acceptor.

Each of the derivatives inhibits *Streptococcus pneumoniae* in a dose-dependent manner. At the highest concentration, compound C (23 mm) has the greatest activity among the synthesized

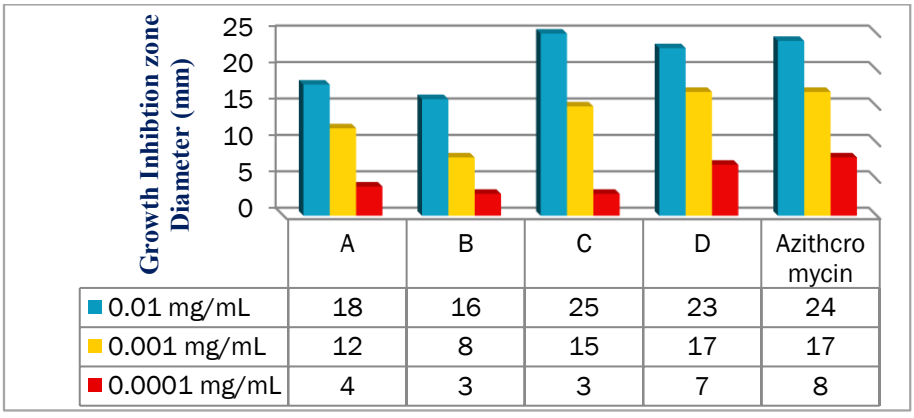
derivatives, followed by derivative D (20 mm), derivative B (17 mm), and A (15 mm). The optimal standard is 25 mm azithromycin. The inhibitory zones of derivative A significantly decrease at middle and low dosages, indicating less activity persistence. The derivative C is the most promising derivative against S. pneumonia, demonstrating sustained suppression comparable to the reference antibiotic at elevated doses, as shown in **Figure 10.**



	A	B	C	D	Azithcro mycin
0.01 mg/mL	15	17	23	20	25
0.001 mg/mL	9	10	15	13	18
0.0001 mg/mL	2	4	9	8	9

Figure 10: Synthesized derivatives activity of against *Streptococcus pneumonia.*

Each synthesized derivative has concentration-dependent *Bacillus subtilis* antibacterial activity. At 0.1 dosage, derivative C (25 mm) and derivative D (23 mm) had the largest inhibitory zones, reaching azithromycin (24 mm). Both derivative A (18 mm) and derivative B (16 mm) demonstrated modest action at equal doses. At concentrations of 0.001 and 0.00001, inhibition zones markedly decrease for all derivatives, indicating reduced efficacy at lower doses. Derivatives C and D exhibit superior antibacterial efficacy compared to derivatives A and B, suggesting enhanced interaction with bacterial targets, as shown in **Figure 11.**



	A	B	C	D	Azithcro mycin
0.01 mg/mL	18	16	25	23	24
0.001 mg/mL	12	8	15	17	17
0.0001 mg/mL	4	3	3	7	8

Figure 11: Antibacterial activity of synthesized derivatives against *Bacillus subtilis.*

This figure demonstrates A's concentration-dependent cytotoxicity against PC-3 cells. Cell viability decreases from 99.69% in the control group to 59.26% and 44.51% at 20 and 40 ppm. At the maximum dosage, viability is reduced to 4.99% by high dosages (80–320 ppm). This notable decline seems to have the potential to impede development and cause cell death. Because of its consistent trend throughout concentrations, chemical A may combat prostate cancer at high doses, as shown in **Figures 12 and 13.**

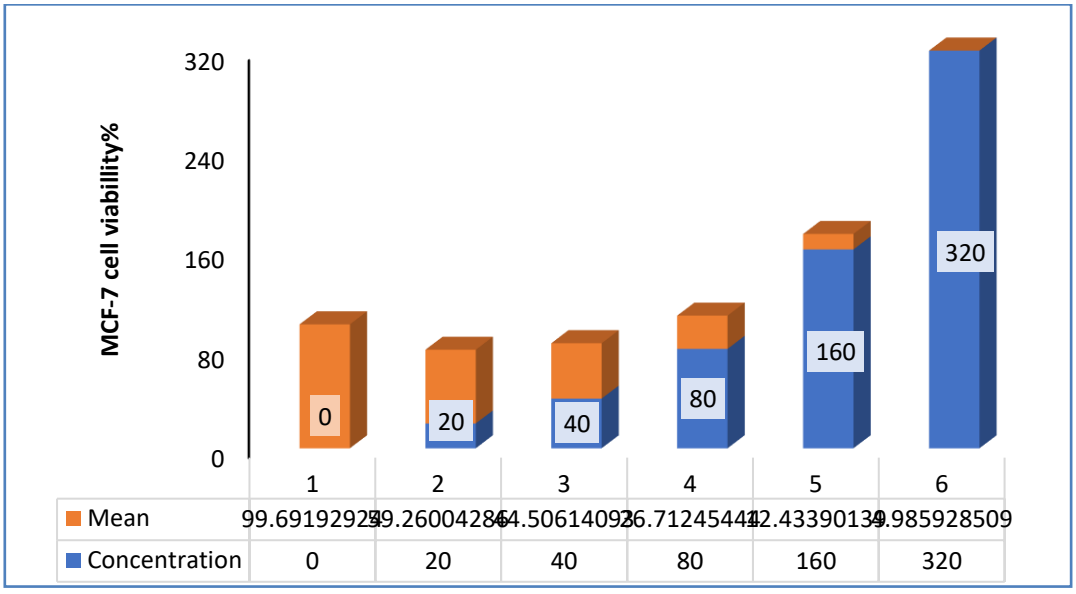


Figure 12: Cytotoxicity of MCF-7 Cells to increasing concentrations of derivative A.

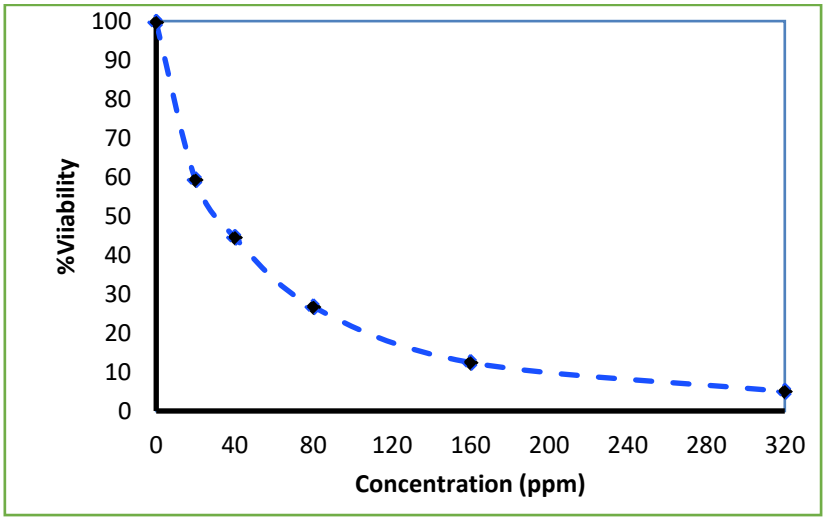


Figure 13: Dose response curve illustrating the cytotoxic effect of derivative A on MCF-7 Cells.

Concentration-dependent Compound C cytotoxicity against MCF-7 cells. Control group cell viability remains almost unaltered, indicating normal cell growth. Growth inhibition is seen between 20 and 40 ppm, when viability reduces to 61% and 50%. Higher dosages reduce viability to 33.5% at 80 ppm and 8% at 320 ppm. This slow fall reveals that derivative C restricts

cell proliferation and may kill cells at high doses. The derivative C has exceptional antitumor potential against MCF-7 cells, as shown in **Figures 14 and 15**.

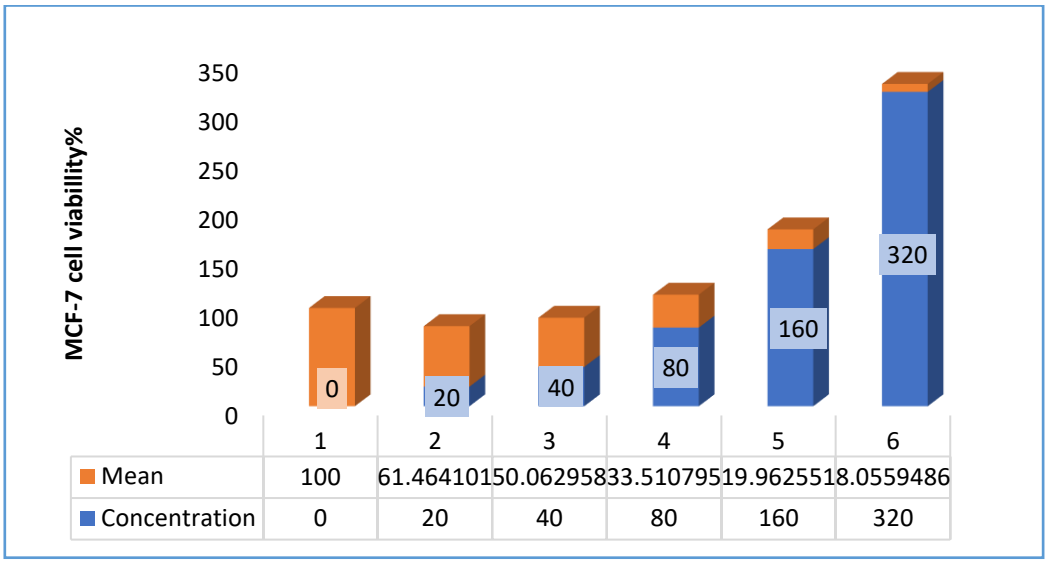


Figure 14: Cytotoxicity of MCF-7 Cells to increasing concentrations of derivative C.

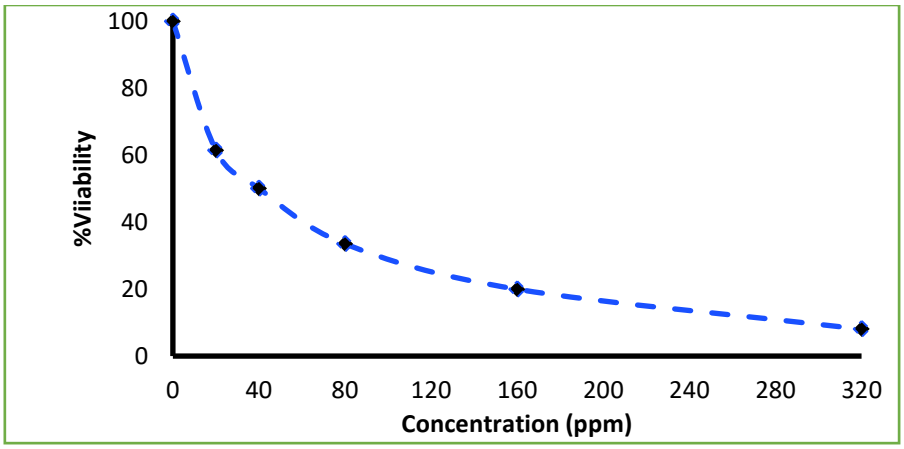
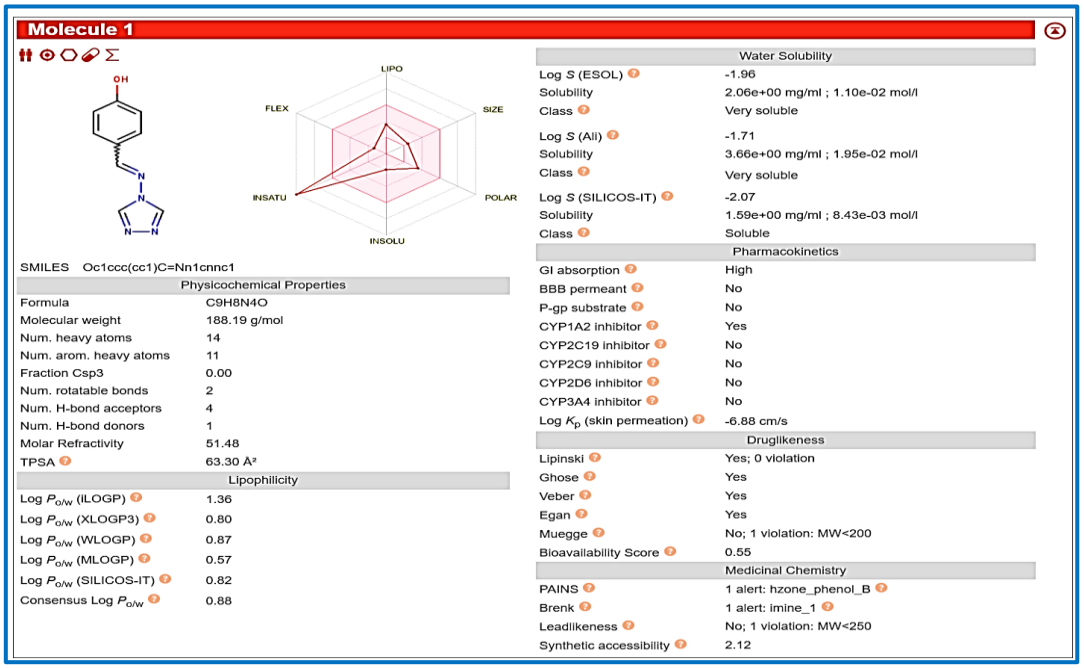


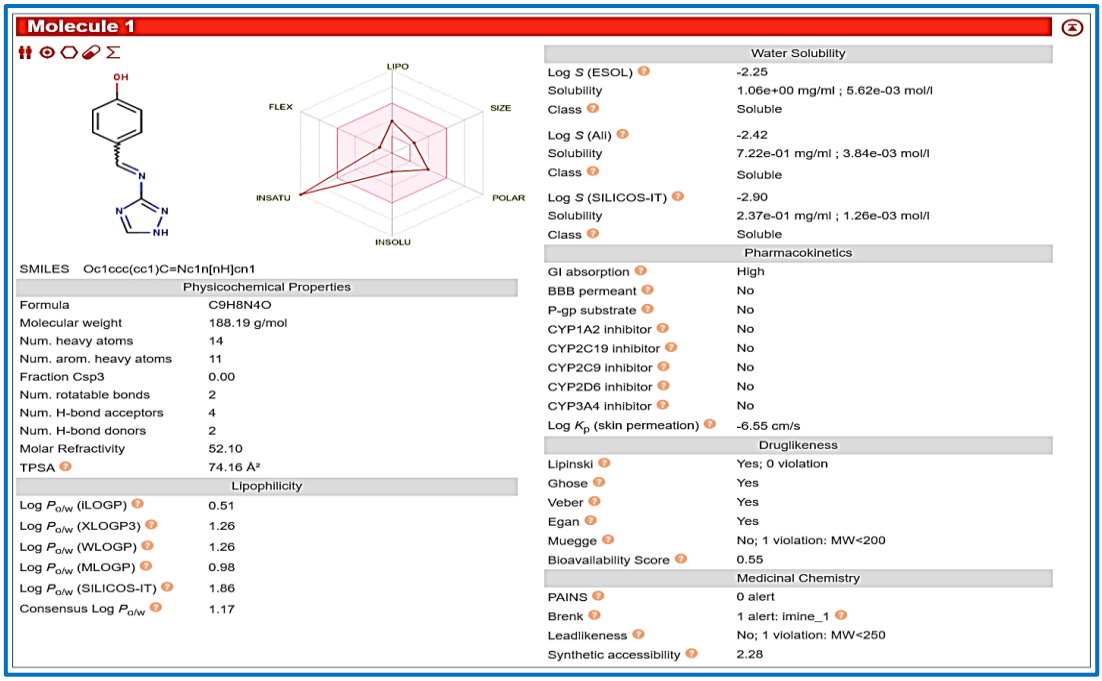
Figure 15: Dose response curve illustrating the cytotoxic effect of derivative C on MCF-7 Cells.

The predicted ADMET profiles for derivatives A-D (**Schemes 3-6**) show drug-likeness and pharmacokinetics. All derivatives have molecular weights below 250 g/mol and pass Lipinski's rule of five without exception, indicating oral drug-like characteristics. The consensus LogP values of 1.1–1.8 imply balanced lipophilicity, which improves membrane permeability and water solubility. All compounds are predicted to be water-soluble, which aids formulation and absorption. Pharmacokinetic estimates imply oral uptake due to high gastrointestinal absorption for all derivatives. Anticancer and antibacterial compounds are unlikely to cross the blood-brain barrier, reducing central nervous system side effects. Without P-glycoprotein substrate behavior, efflux-mediated drug resistance is unlikely. Importantly, the compounds do not inhibit critical cytochrome P450 enzymes, indicating low metabolic drug-drug interactions. The

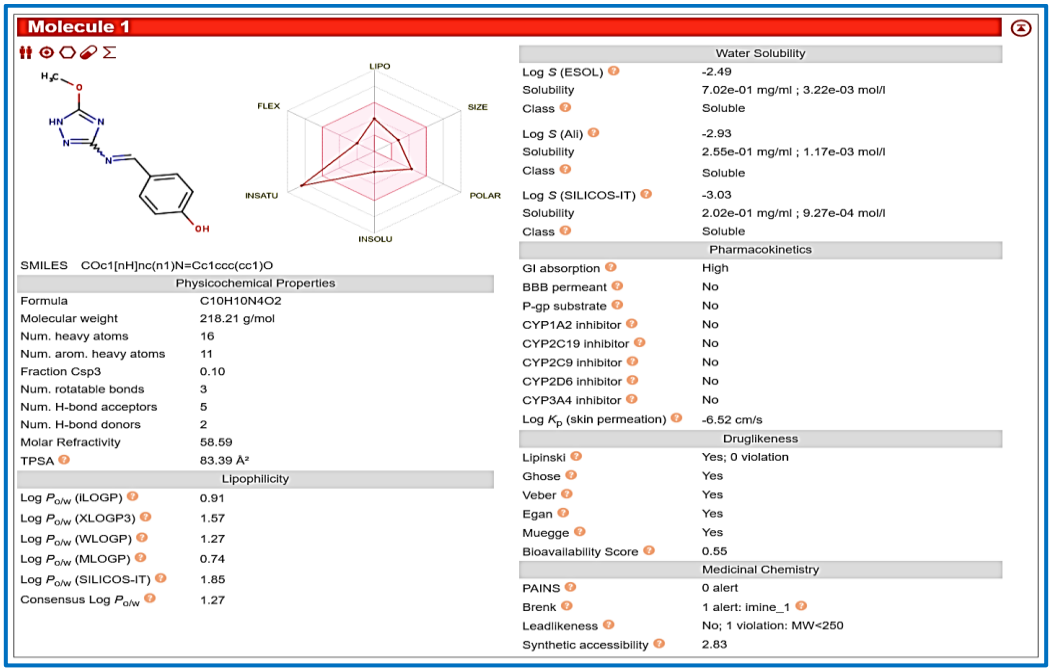
absence of PAINS alerts in medicinal chemistry improves confidence in experimental data's biological relevance, whereas the imine functionality Brenk alarm is expected and chemically justified. ADMET analysis confirms experimental findings and reveals that the produced triazole-imine compounds have appropriate pharmacokinetic properties for optimization and biological evaluation.



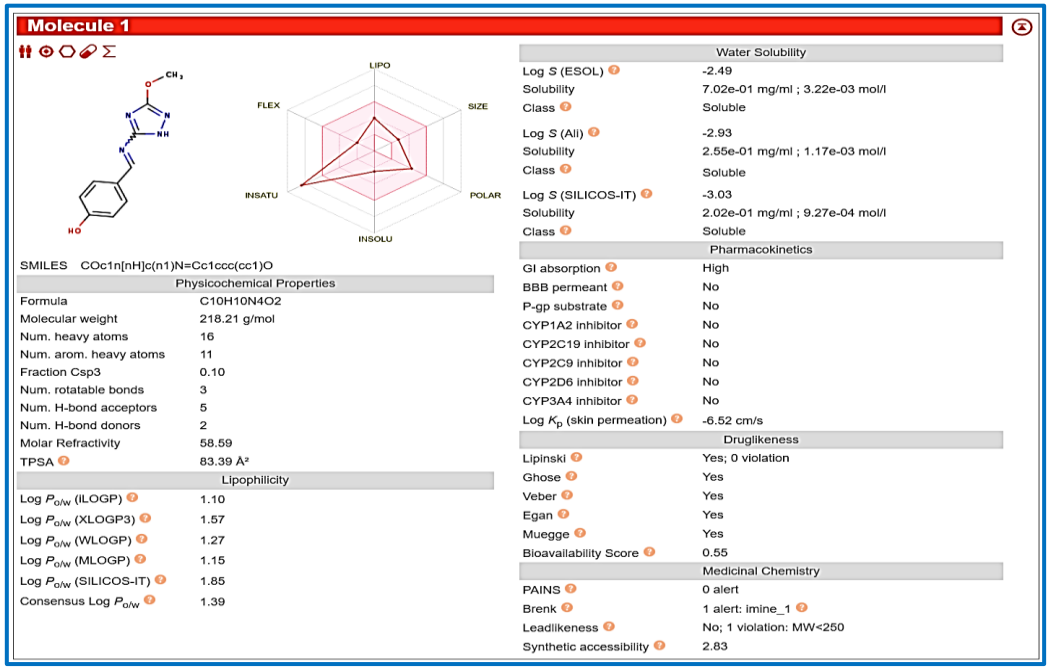
Scheme 3: SwissADME Prediction for derivative A.



Scheme 4: SwissADME Prediction for derivative B.



Scheme 5: SwissADME Prediction for derivative C.



Scheme 6: SwissADME Prediction for derivative D.

5. Conclusion

This study shows that triazole–imine derivatives are versatile and physiologically active heterocyclic compounds. Successful synthesis and spectroscopic analysis demonstrate moderate structural modification of triazole-based Schiff bases. Thus, substituent type and concentration considerably alter antibacterial and cytotoxic properties, as compound C suppresses bacteria better while compound A kills PC-3 and MCF-7 cells. Molecular docking studies show that ligand-protein interactions in the 8RZX binding pocket survive via hydrogen bonding and π–π stacking. These data

suggest electrical dispersion and aromaticity affect biological performance. Although promising, the study requires in vivo confirmation and selectivity testing against normal cells. The next research will focus on biological applications such antifungal screening, mechanistic apoptosis, and in vivo anticancer testing. Molecular dynamics simulations are essential to study ligand stability over time. Expanding the compound library and relating physicochemical aspects to biology may enhance structure–activity connections. This research provides a solid experimental and theoretical foundation for rationally constructing triazole–imine-based therapies.

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