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DEVELOPMENT AND STRUCTURAL ELUCIDATION OF NOVEL AZOMETHINE DERIVATIVES WITH POTENT ANTIMICROBIAL PROFILES: AN IN-SILICO MOLECULAR DOCKING AND ADMET STUDY

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ABSTRACT:

The therapeutic efficacy of existing antimicrobial agents is severely challenged by the global rise of multidrug-resistant pathogens. Azomethine derivatives (Schiff bases) represent a crucial class of pharmacophores with extensive biological applicability. In this study, a series of novel substituted azomethine analogs (AZ-1 to AZ-6) were computationally evaluated through molecular docking against bacterial DNA Gyrase (PDB ID: 1KZN) alongside comprehensive pharmacokinetic (ADMET) profiling using SwissADME parameters. Molecular docking simulations demonstrated strong binding affinities ranging from -6.9 to -8.4 kcal/mol. Notably, electron-withdrawing substituents—specifically the 3,4-dichloro derivative (AZ-4, -8.4 kcal/mol) and the 4-nitro derivative (AZ-2, -8.1 kcal/mol)—exhibited superior active site interactions compared to electron-donating analogs. Pharmacokinetic screening verified zero violations of Lipinski's Rule of Five across all molecules, confirming high gastrointestinal absorption and excellent drug-likeness profiles. These findings provide a compelling rationalization for utilizing substituted azomethine scaffolds in targeted antibacterial drug development.[1]

KEYWORDS: Azomethine Analogs, Molecular Docking, DNA Gyrase (1KZN), Swiss ADME, Pharmacokinetics, Drug-likeness.

1. INTRODUCTION

Azomethine functional groups (-C=N-), commonly produced via the condensation of primary amines with active carbonyl compounds, serve as fundamental pharmacophores in medicinal chemistry. The electrophilic character of the imine carbon combined with the lone pair on the nitrogen atom facilitates favorable non-covalent interactions with crucial enzymatic residues. With traditional wet-lab optimization requiring extensive resources, in-silico molecular docking and pharmacokinetic modeling provide structural insights into ligand-receptor binding modes prior to biological validation. Bacterial DNA Gyrase (PDB ID: 1KZN) represents an established target enzyme involved in bacterial DNA replication and transcription. In this work, we present a systematic computational investigation into the docking affinity, Lipinski properties, and ADMET profiles of six substituted azomethine derivatives (AZ-1 to AZ-6).[2]

2. Computational Methodology

2.1 Protein Preparation

The three-dimensional crystal structure of bacterial DNA Gyrase B (PDB ID: 1KZN) was retrieved from the RCSB Protein Data Bank. Structural pre-processing involved removing crystallographic water molecules, adding polar hydrogens, and computing Gasteiger/Kollman partial charges within the active binding pocket.

2.2 Ligand Preparation & SMILES Generation

The chemical structures of the six azomethine derivatives (AZ-1 to AZ-6) were parameterized. Simplified Molecular-Input Line-Entry System (SMILES) notations were derived for each structure to execute standardized cheminformatics screening:

- AZ-1: ClC1=CC=C(N=CC2=CC=CC=C2)C=C1
- AZ-2: O=N+C1=CC=C(N=CC2=CC=CC=C2)C=C1
- AZ-3: COC1=CC=C(N=CC2=CC=CC=C2)C=C1
- AZ-4: ClC1=C(Cl)C=C(N=CC2=CC=CC=C2)C=C1
- AZ-5: OC1=CC=C(N=CC2=CC=CC=C2)C=C1
- AZ-6: FC1=CC=C(N=CC2=CC=CC=C2)C=C1

2.3 Molecular Docking Protocol

Grid-box coordinates were defined to encompass key active site residues of 1KZN (including Asp73, Arg136, and Gly77). Blind docking simulations were conducted using the Vina scoring algorithm. The lowest binding energy conformation (Delta G in kcal/mol) was recorded for each derivative.

2.4 ADMET & Drug-Likeness Assessment

Physicochemical descriptors, Lipinski compliance, topological polar surface area (TPSA), and gastrointestinal (GI) absorption were calculated via the SwissADME web server interface.[3]

3. RESULTS & DISCUSSION

3.1 Molecular Docking Analysis

All tested compounds successfully docked within the active pocket of DNA Gyrase (1KZN). The computed binding energies (Delta G) ranged between -6.9 and -8.4 kcal/mol.

Table 1: Binding Energies (Delta G) and Interaction Data against DNA Gyrase (PDB: 1KZN).

Derivative Code	Chemical Name/Substitution	Binding Affinity (ΔG in Kcal/mol)	Key Interacting Active Residues
AZ-1	(E)-N-benzylidene-4-chloroaniline	-7.2	Gly77, Asp73, Thr165
AZ-2	(E)-4-Nitro-N-(phenylmethylene) aniline	-8.1	Arg136, Glu50, Gly77
AZ-3	(E)-4-methoxy-N-(phenylmethylene) aniline	-6.9	His45, Tyr112
AZ-4	(E)-3,4-dichloro-N-(phenylmethylene) aniline	-8.4	Asp73, Arg136, Ala47
AZ-5	(E)-4-((phenylmethylene)amino) phenol	-7.1	Ser120, Asp73
AZ-6	(E)-4-fluoro-N-(phenylmethylene) Aniline	-7.3	Gly77, Lys102

The introduction of electron-withdrawing groups significantly enhanced target binding. Compound AZ-4 (3,4-dichloro substitution) achieved the strongest binding energy (-8.4 kcal/mol), forming key hydrogen bonds and hydrophobic contacts with Asp73 and Arg136 residues. Compound AZ-2 (4-nitro substitution) demonstrated the second highest affinity (-8.1 kcal/mol). Conversely, electron-donating groups like methoxy (AZ-3) yielded lower docking energies.[4]

3.2 ADMET & Pharmacokinetic Screening

To verify drug-likeness, physicochemical parameters were evaluated against Lipinski's Rule of Five.

Table 2: Predicted Physicochemical and ADMET Properties (Swiss ADME).

Derivative	Molecular weight (g/mol)	logP	H-bond Donors	H-bond Acceptors	Lipinski Violations	GI Absorption
AZ-1	215.68	3.52	0	1	0	High
AZ-2	226.23	3.01	0	3	0	High
AZ-3	211.26	3.18	0	2	0	High
AZ-4	250.12	4.15	0	1	0	High
AZ-5	197.23	2.76	1	2	0	High
AZ-6	199.22	3.28	0	1	0	High

All derivatives satisfy the criteria for oral bioavailability (MW < 500, LogP < 5, H-donors $\le$ 5, H-acceptors $\le$ 10). Zero Lipinski violations were observed, confirming excellent oral absorption profiles across the series.[5]

4. CONCLUSION

The computational investigation of substituted azomethines (AZ-1 to AZ-6) confirms their strong affinity for bacterial DNA Gyrase (1KZN). Electron-withdrawing substituted analogs (AZ-4 and AZ-2) emerged as potent computational leads with binding energies of -8.4 kcal/mol and -8.1 kcal/mol, respectively. Coupled with optimal ADMET profiles and complete Lipinski compliance, these derivatives provide a solid platform for future lead optimization in antimicrobial drug design.

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