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# Design, synthesis, molecular docking, and ADMET evaluation of heterocyclic compounds as anticancer and antibacterial agents

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### Abstract

Heterocyclic Schiff base derivatives have various biological functions and have garnered interest. Three new Schiff base derivatives (R1-R3) were synthesized by condensation of 2-amino-5-chlorobenzophenone with aromatic aldehydes in this work. FTIR and <sup>1</sup>H-NMR spectroscopy confirmed the successful production of the azomethine (C=N) bond in the synthesized imine derivatives. Molecular docking was used to assess biological activity against Dihydrofolate Reductase (DHFR, PDB ID: 1RX2). The docking findings showed that derivative R3 had the greatest binding affinity (-6.49306 kcal/mol), followed by synthesized derivatives R1 and R2. Agar diffusion was used to test *Staphylococcus aureus* and *E. coli* for antibacterial activity. Derivative R3 had the greatest antibacterial activity, inhibiting *S. aureus* and *E. coli* with 33 and 19 mm zones, respectively, surpassing azithromycin at the measured dose. The MTT test cytotoxicity against breast cancer MCF-7 cell line showed concentration-dependent antiproliferative effects. Cytotoxicity was higher in derivative R3, which had an IC<sub>50</sub> of 122.8 ppm compared to 161 ppm for synthesized derivative R1. The dimethylamino-substituted derivative R3 has excellent antibacterial and anticancer activities and may be a lead molecule for pharmaceutical development.

**Keywords:** Bacteria, heterocyclic, schiff base, molecular docking

### Introduction

Heterocyclic compounds, or heterocycles, are organic chemicals with a ring-like structure and heteroatoms <sup>[1]</sup>. Cyclic and acyclic heterocycles exist. Heterocycles have physico-chemical characteristics different from carbon ring analogues because they contain heteroatoms instead of carbon atoms <sup>[2]</sup>. Heterocycles have agrochemical, pharmaceutical, and veterinary applications <sup>[3-5]</sup>. Sanitisers, antioxidants, copolymers, corrosion inhibitors, dyestuff, etc. employ such chemicals <sup>[6]</sup>. Heterocycles are used to make several organic chemicals. Many natural substances, including alkaloids, morphine, vinblastine, and reserpine, and antibiotics like cephalosporin and penicillin, have heterocyclic components <sup>[7]</sup>. Schiff bases are important heterocyclic compounds due to their structural variety and easy production <sup>[8]</sup>. The azomethine functional group is synthesized from a primary amine coupled to an aldehyde to prepare Schiff bases, and this imine bond is essential to a basic pharmacophore with several biological functions <sup>[9]</sup>. Schiff base derivatives have been widely researched as antibacterial and anticancer drugs due to metal ion coordination <sup>[10]</sup>.

Given antibiotic resistance and rising cancer rates, new safe and effective treatments are required, and the mechanisms of action of newly synthesized medicines and ligand-protein interactions predicted via molecular docking <sup>[11, 12]</sup>. Microbial and cancer cells need dihydrofolate reductase (DHFR) for folate metabolism and DNA biosynthesis, making it a frequent therapeutic target <sup>[13, 14]</sup>.

This study synthesizes Schiff base compounds R1-R3 from aromatic aldehydes and 2-amino-5-chlorobenzophenone, and these compounds R1-R3 characterization and molecular docking with DHFR (PDB ID: 1RX2), antibacterial and cytotoxicity test against MCF-7 cell line were undertaken to assess the synthesized compounds as antimicrobial and anticancer drugs.

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## Methodology

### Synthesis of Schiff base derivatives (R1-R4)

Through reacting identical moles of various aldehyde compounds with 2-Amino-5-chlorobenzophenone, which were categorized as primary amines, a new different group of imine derivatives (R1-R4) were synthesized, according to Jaafar, M. R., *et al.* (2024) [15]. After dissolving 0.1 mole of 2-Iodobenzaldehyde, 4-Iodo-3-methylbenzaldehyde, and 4-(Dimethylamino)benzaldehyde in 15 mL of absolute ethanol, add two to three drops of glacial acetic acid, add 2-Amino-5-chlorobenzophenone, and reflux for three hours. After cooling to room temperature, the solutions are filtered to extract the precipitates [16]. As shown in Scheme 1, create derivative R1 from 2-Iodobenzaldehyde, derivative R2 from 4-Iodo-3-methylbenzaldehyde, and derivative R3 from 4-(Dimethylamino)benzaldehyde.

The synthetic derivative R1's physical characteristics included a yellow precipitate and a melting point of 243°C. On the other hand, derivative R1 had a yellow color and a melting point of 227°C, whereas derivative R3 had a light yellowish color and a melting temperature of 251°C.

### 2.3 Molecular docking

The 3D structures of the newly synthesized Schiff bases R1-R3 were created using ChemDraw Ultra 12.0 and then subjected to energy minimization [17]. The semi-empirical AM1 method in HyperChem 8.08 was used to pre-optimize the structures [18]. In order to evaluate ligand affinity, the optimized structures were combined into a single database using MOE software (2022) [19]. Hydrogen atoms are integrated, missing bonds are fixed, and the water molecule is kept at the active site to facilitate hydrogen interaction with ligands. The Dihydrofolate Reductase (DHFR, PDB ID: 1RX2) protein analysis is also included [20], and docking and scoring are carried out using the Molecular Operating Environment software (MOE, 2019) [21].

### 2.4 Antimicrobial evaluation of synthesized Schiff base (R1-R3)

The cup-plate agar diffusion technique was used to assess the antibacterial activity of the synthesized Schiff base R1-

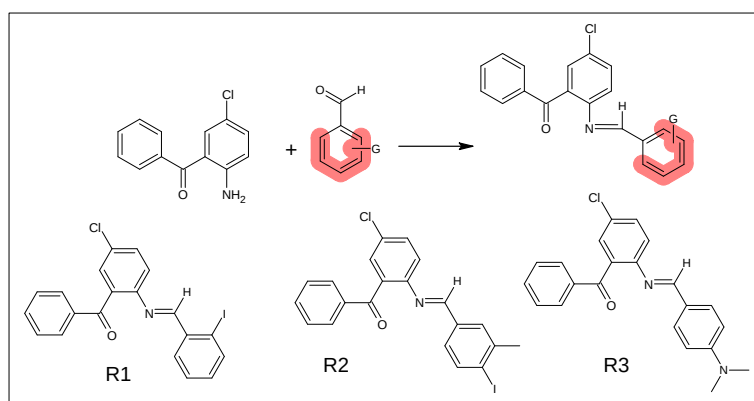
R3 [22]. Clinical isolates of *Staphylococcus aureus* and *Escherichia coli* were among the bacterial strains against which these synthetic derivatives were evaluated at different doses of 0.1, 0.001, and 0.00001 mg/mL. Mueller-Hinton agar plates prepared with 12 mm dissolved in DMSO were used to inoculate the bacteria [23]. After dissolving the reference medication azithromycin in sterile distilled water, the dish was incubated for 48 hours at 37 °C [24].

### 2.5 Cytotoxicity by MTT assay

The MTT test was used to evaluate the cytotoxicity of the synthesized Schiff bases R1 and R3 against the human cell line MCF-7. Following incubation, cells were given synthetic derivatives at doses of 0, 20, 40, 80, 160, and 320 µg/mL using a 2-fold serial dilution. After incubation, remove the supernatant and dissolve formazan in each well with 100 µL of DMSO to preserve crystals. Five minutes of moderate shaking caused the plates to melt. The half-maximal inhibitory concentration of the derivatives was determined by statistical analysis, and absorbance at 575 nm was measured using the ELISA microplate reader (Bio-Rad, Germany), with optical density values indicating cell viability [25, 26].

## Results and Discussion

Scheme 1 demonstrates the synthesis of Schiff base derivatives R1-R3, and these target compounds were prepared by condensation of 2-amino-5-chlorobenzophenone and aromatic aldehydes such as 2-iodobenzaldehyde, 4-iodo-3-methylbenzaldehyde, and 4-(dimethylamino)benzaldehyde under catalytic concentrations of glacial acetic acid. A nucleophilic carbinolamine intermediate is formed by a nucleophilic attack of amino group on carbonyl carbon of aldehyde derivative. The thermodynamically stable imine bond is produced upon proton transfer and water molecule removal to synthesize Schiff base derivatives R1-R3. The addition of electron-donating and electron-withdrawing substituents on aromatic aldehydes affect reaction efficiency, electronic properties, and biological activity [27].



**Scheme 1:** Routes of Schiff base derivatives R1-R3.

These synthesized derivatives characterization by used FTIR ( $\text{cm}^{-1}$ ), as shown in Figures 1-3. The FTIR spectrum of derivative R1, showed a peak of carbonyl amide at 1691, imine group at 1631, C-H of aromatic ring at 3001, C-C at 1003 and C-N at 1172. FTIR spectrum of derivative R2, showed a peak of imine group at 1640, C-H of aromatic ring at 3095, C-C at 1068 and C-N at 1186. While FTIR

spectrum of derivative R3, showed a peak of imine group at 1613, C-H of aromatic ring at 3056, C-C at 1042 and C-N at 1102 [28], as shown in Figure 1.

$^1\text{H-NMR}$  (ppm) used DMSO- $d_6$  as solvent, as shown in Figures 2-4, and the spectrum of the derivative R1 showed bands at 7.13-7.76 for protons of aromatic ring as a multiplet and 8.91 for imine proton  $\text{CH}=\text{N}$  as a singlet. The

derivative R2 showed bands at 7.39-7.77 for protons of aromatic ring as a multiplet and 8.77 for imine proton CH=N as a singlet. Finally, the derivative R3 showed bands

7.39-8.21 for protons of aromatic ring as a multiplet and 8.58 for imine proton CH=N as a singlet <sup>[29]</sup>.

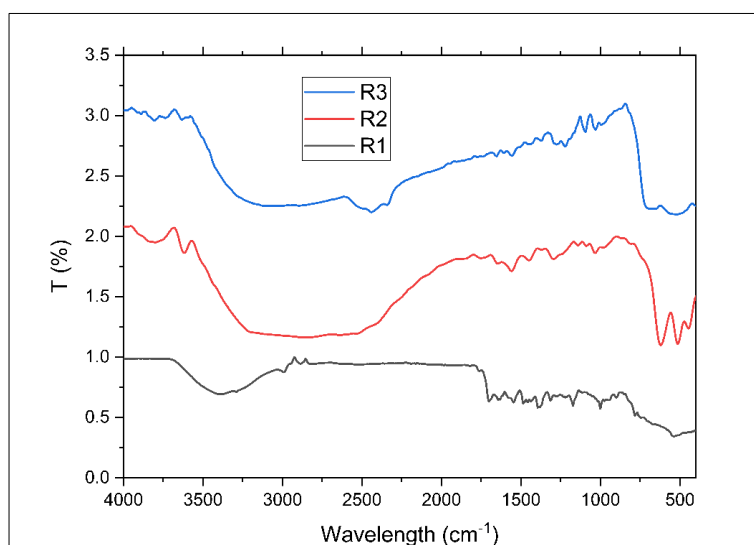


Fig 1: FTIR spectrum of synthesized derivatives R1-R3.

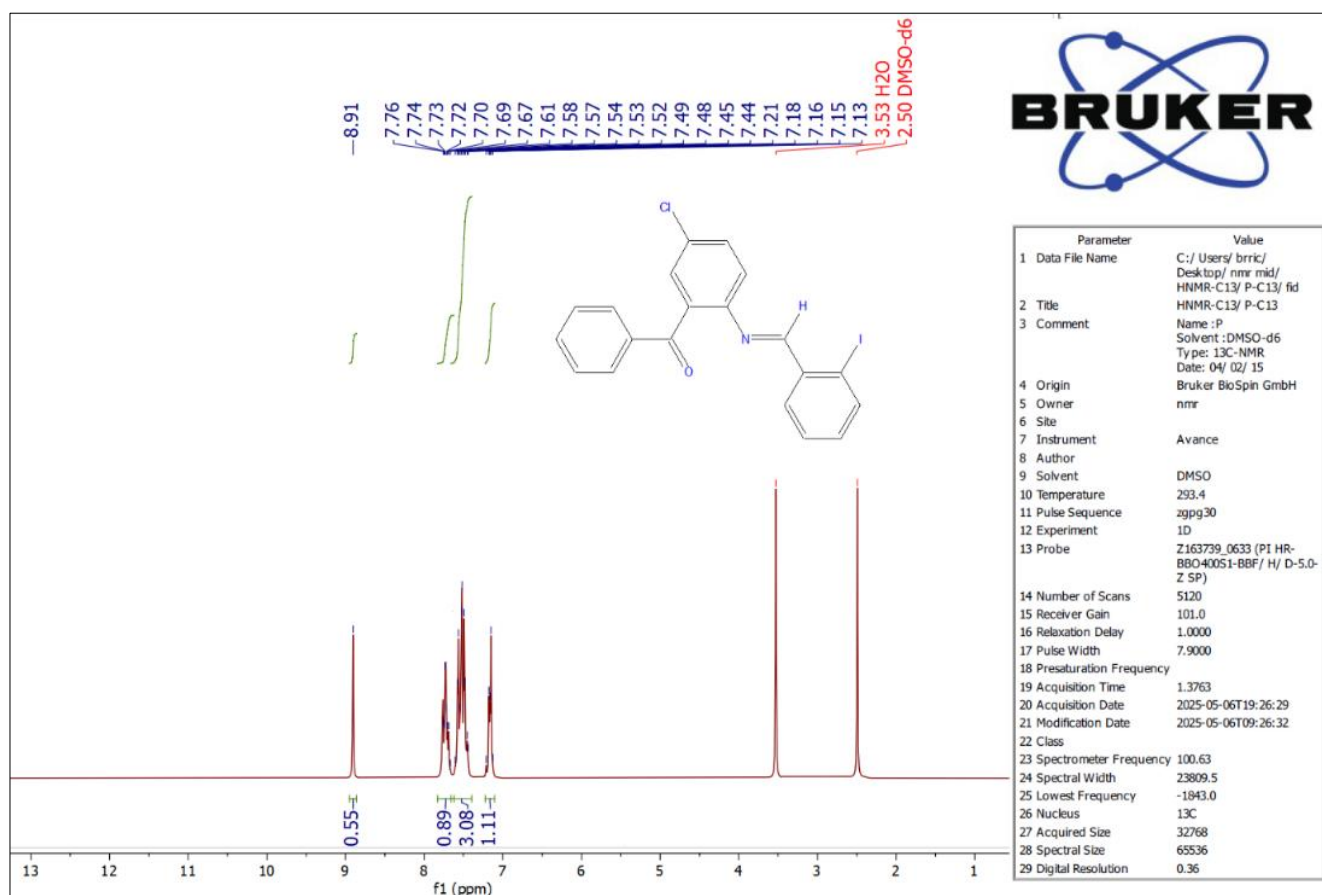
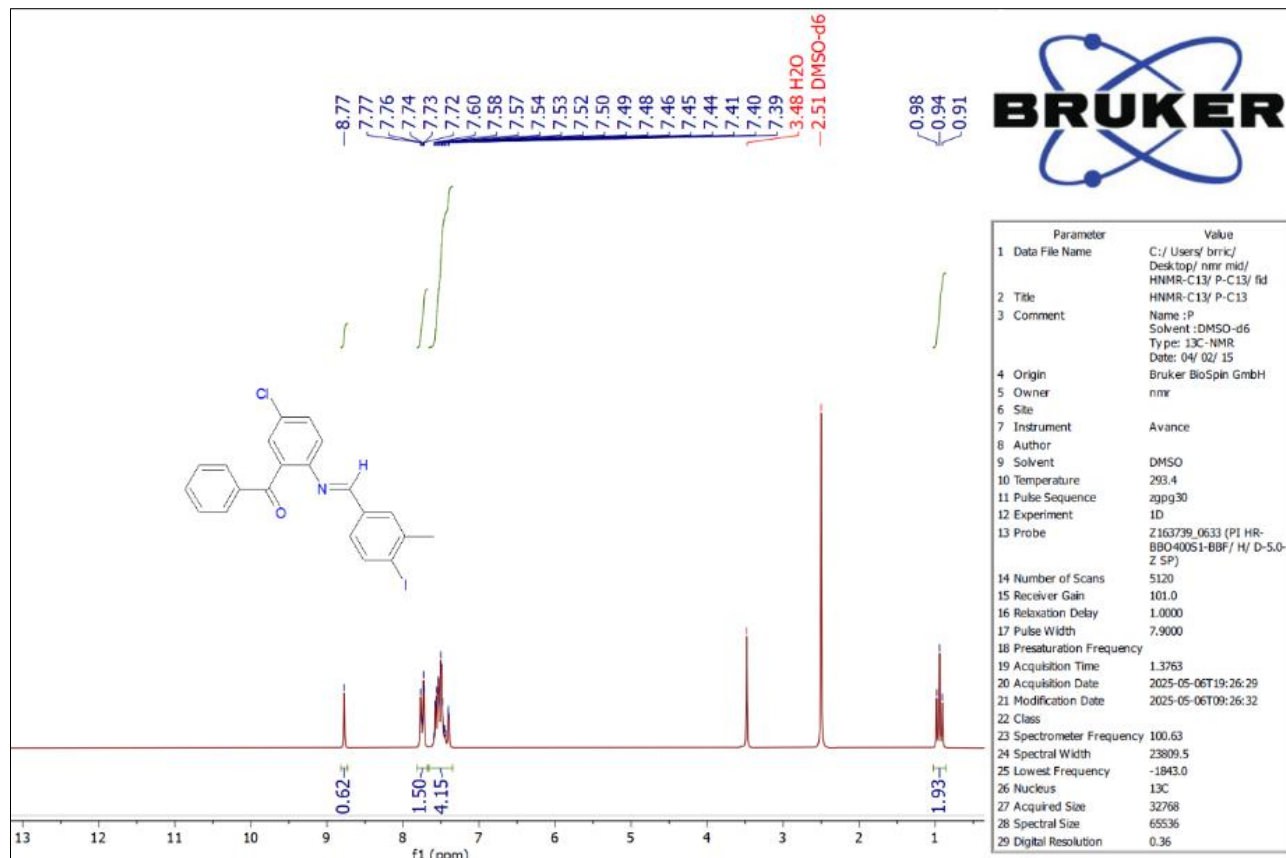
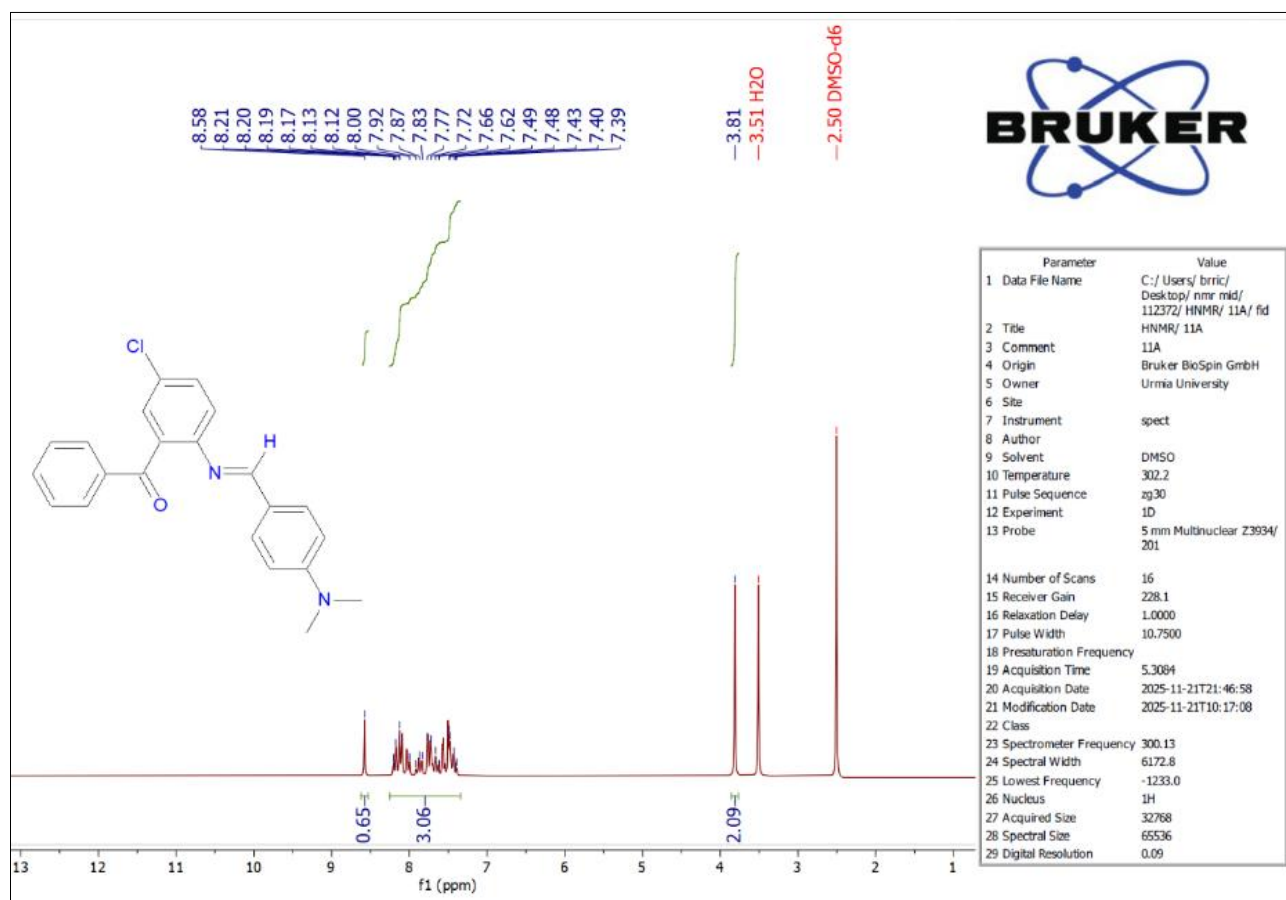


Fig 2: <sup>1</sup>H-NMR spectrum of derivative R1.

Fig 3: <sup>1</sup>H-NMR spectrum of derivative R2.Fig 4: <sup>1</sup>H-NMR spectrum of derivative R3.

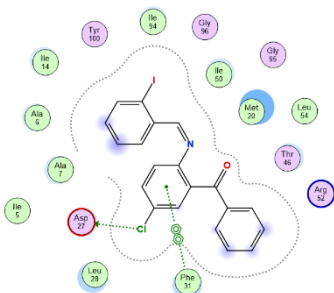
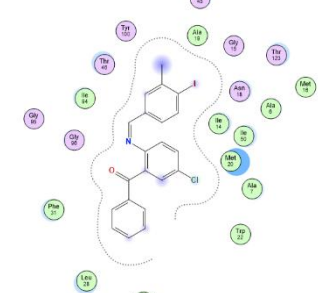
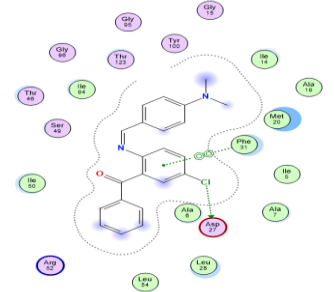
The imine derivative R3 had the greatest binding affinity with score as -6.49306 kcal/mol, indicating a favorable

interaction with the active site of DHFR protein. The most significant amino acid residues, Met20, Phe31, Ala7, and

Asp27, interacted hydrophobically with the ligand to stabilize it in the binding pocket, with the RMSD as 2.63 Å was slightly over the threshold, the docking score showed a strong ligand-enzyme contact. The docking score as -6.25271 kcal/mol and the RMSD value as 1.82 Å indicate a stable binding conformation for the synthesized derivative R1, and this ligand interacted with crucial active-site residues including Asp27, Phe31, Ile5, Ile14, Ala7, and Leu28 to better fit the catalytic pocket of DHFR. Finally, the

synthesized derivative R2, with a docking score as -5.9578 kcal/mol, exhibited the lowest binding affinity among all examined derivatives. Conversely, its lowest RMSD as 0.99 Å suggests high structural stability. Due to limited favorable interactions with catalytic residues, the binding energy may be lower than synthesized derivatives R1 and R3. These docking tests show all synthesized variants bind active site optimally of DHFR, and docking score determines binding affinity order: R3 > R1 > R2.

**Table 1:** Molecular docking results of synthesized derivatives R1-R3 with Dihydrofolate reductase 1RX2.

| Compound No. | S        | RMSD_refine | Interaction                                                                          |
|--------------|----------|-------------|--------------------------------------------------------------------------------------|
| R1           | -6.25271 | 1.815832    |    |
| R2           | -5.9578  | 0.993364    |   |
| R3           | -6.49306 | 2.625737    |  |

Figures 5 and 6 show the antibacterial activity of the synthesized Schiff base derivatives R1-R3 against *Staphylococcus aureus* and *E. coli*. All substances showed concentration-dependent antibacterial activity with maximal inhibition zones at 0.1 mg/mL. Derivative R3 had 33 mm

and 19 mm inhibitory zones on *S. aureus* and *E. coli*, respectively, greater than azithromycin (28 and 15 mm). R1 and R2 compounds have moderate antimicrobial activity. R3 > R1 > R2 indicated that the dimethylamino-substituted derivative had more antibacterial potential.

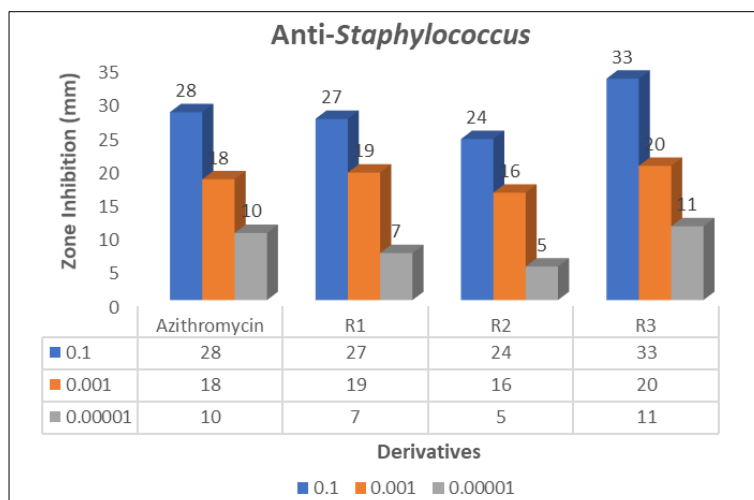


**Fig 5:** Biological activity of synthesized derivatives R1-R3 against *Staphylococcus*.

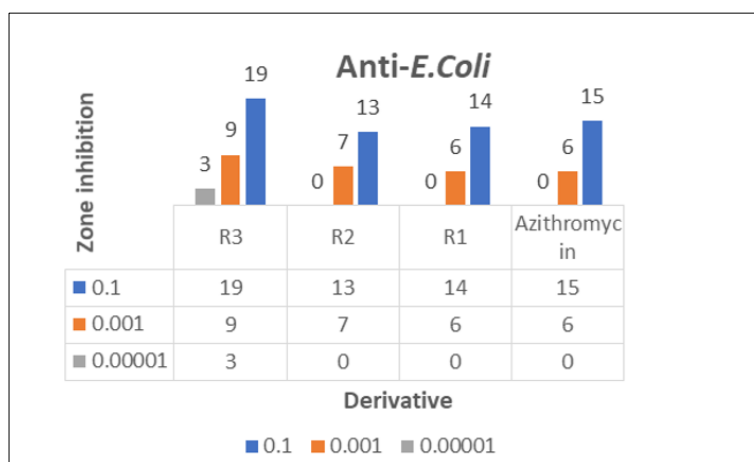


**Fig 6:** Biological activity of synthesized derivatives R1-R3 against *E. Coli*.

Figures 7-10 show that the synthesized Schiff base derivatives R1 and R3 are cytotoxic to MCF-7 breast cancer cells. Both compounds demonstrated concentration-dependent antiproliferative action that decreased cell viability. The IC<sub>50</sub> of derivative R3 was 122.8 ppm,

compared to 161 ppm for derivative R1. This increased its anticancer effects. R3 lowered cell viability to 30% at 320 ppm, whereas R1 exhibited 36%. R3 may be more cytotoxic owing to its electron-donating dimethylamino group, which enhances cell absorption and biological target engagement.

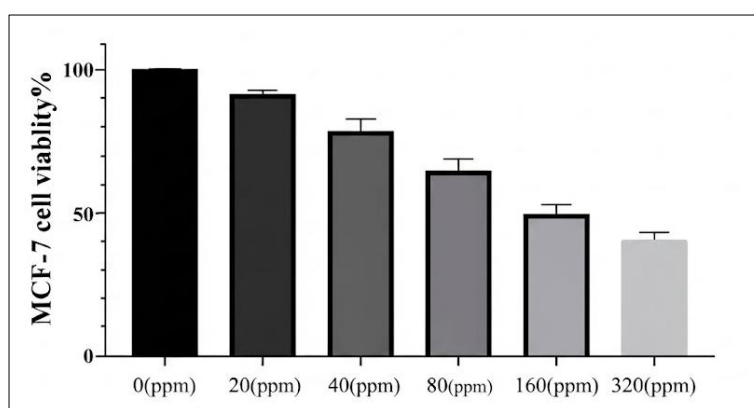


**Fig 7:** Synthesized derivative R1 effect on MCF-7 cell line.

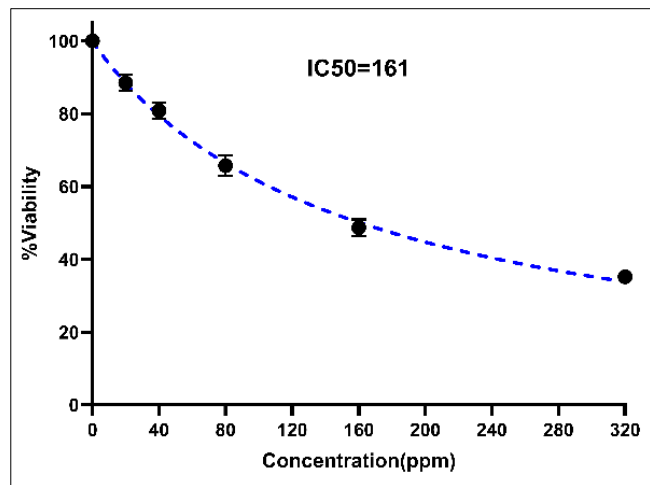


Fig 8: IC50 value of derivative R1 against MCF-7 cell line.

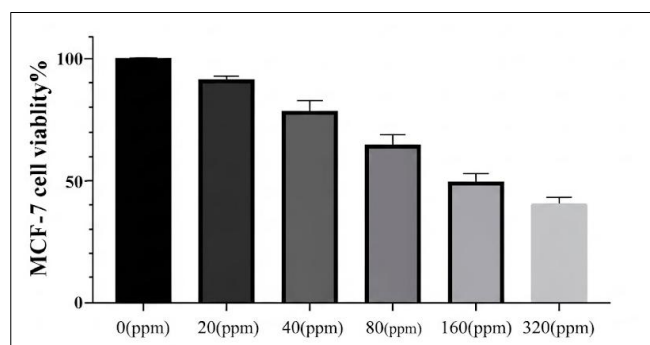


Fig 9: Synthesized derivative R3 effect on MCF-7 cell line.

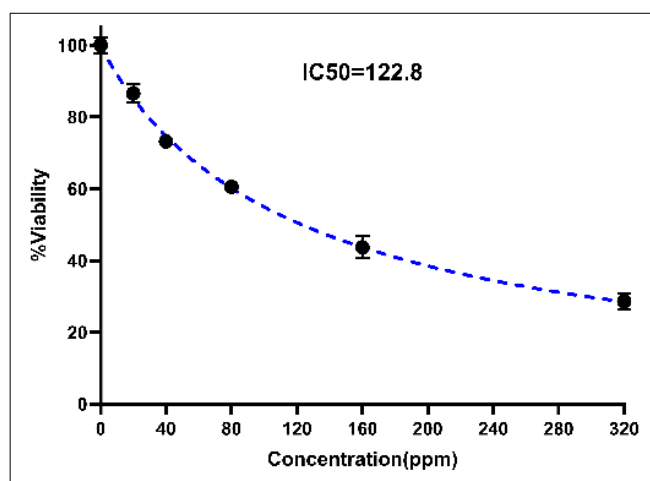


Fig 10: IC50 value of derivative R3 against MCF-7 cell line.

The successful synthesis of Schiff base derivatives R1-R3 was validated using FTIR and  $^1\text{H-NMR}$  studies, and target synthesized derivatives were confirmed by the presence of imine ( $\text{C}=\text{N}$ ) absorption bands in FTIR spectra and singlet signals for the azomethine proton in  $^1\text{H-NMR}$  spectra. These results imply that 2-amino-5-chlorobenzophenone and the aromatic aldehydes condensed well.

Molecular docking experiments showed that synthesized derivative R3 has the highest DHFR binding affinity ( $-6.49$  kcal/mol), followed by synthesized derivatives R1 and R2. The electron-donating dimethylamino group raises electron density and boosts enzyme active site contacts, which enhances R3 binding. This observation matches the study's biological findings.

The antibacterial testing showed that R3 inhibited *Staphylococcus aureus* and *Escherichia coli* better than azithromycin at  $0.1$  mg/mL. The synthesized derivative R3, having a lower IC50 ( $122.8$  ppm) than synthesized derivative R1, was more cytotoxic against MCF-7 breast cancer cells. The dimethylamino substituent may increase lipophilicity and cellular penetration, improving synthesized derivative R3's biological performance. According to docking, antibacterial, and cytotoxicity results, derivative R3 is most promising derivative for pharmacological inquiry.

### Conclusion

Three novel Schiff base derivatives R1-R3 were successfully synthesized from 2-amino-5-chlorobenzophenone and different aromatic aldehydes and subsequently characterized using FTIR and  $^1\text{H-NMR}$  spectroscopy. Spectroscopic analyses confirmed the formation of the desired azomethine-containing structures. In this research, the molecular docking studies demonstrated favorable interactions between the synthesized compounds R1-R3 and the DHFR active site, with synthesized derivative R3 exhibiting the strongest binding affinity. Biological evaluation revealed that all synthesized compounds possessed antibacterial activity against both Gram-positive and Gram-negative bacteria in a concentration-dependent manner. Among the tested derivatives, R3 showed the highest antibacterial potency, surpassing the reference drug azithromycin under the studied conditions. Furthermore, cytotoxicity studies against MCF-7 cell line indicated significant antiproliferative activity, with derivative R3 displaying the lowest IC50 value and the greatest reduction in cell viability. The superior biological performance of synthesized derivative R3 may be attributed to the presence of the electron-donating dimethylamino group, which enhances its interaction with biological targets. Overall, the combined spectroscopic, computational, and biological findings identify synthesized derivative R3 as the most promising derivative and support further investigations into its mechanism of action, safety profile, and potential therapeutic applications.

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