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Bioactive Imine-Amoxicillin Hybrids: Dual Antibacterial and Anti-Breast Cancer Potentials Supported by Molecular Docking

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Abstract

Antimicrobial and anticancer drug resistance represent two of the main global challenges for public health and require immediate practical solutions. Drug-resistant cancer chemotherapy and the growing threat posed by antimicrobial-resistant infections represent additional biomedical challenges. Thus, one viable way forward to develop multifunctional candidates with improved biological value is by altering existing drugs through chemical modification. Three imine-amoxicillin hybrids, J1-J3, were synthesized from the condensation of amoxicillin trihydrate with 2,4-dihydroxy-3-propylbenzaldehyde, 3-ethyl-4-hydroxy-5-methylbenzaldehyde, and 2-(3-formyl-4-hydroxyphenyl)acetonitrile. All products were successfully obtained as yellow to yellowish-orange precipitates, and subsequent characterization of the products by FTIR demonstrated that azomethine C=N bands formed during the condensation reactions. FTIR data also revealed the formation of new azomethine bands corresponding to derivatives J1 at 1643, J2 at 1620, and J3 at 1644 cm-1, indicating that Schiff base synthesis occurred. Additionally, docking studies were performed against the 6IIO protein, and the results revealed that synthesized derivatives J1, J2, and J3 possessed favorable docking scores of -7.83371, -8.18972, and -8.1703 kcal/mol, respectively. Derivatives J2 and J3 demonstrated the strongest antibacterial activity against S. pyogenes and B. subtilis, producing inhibition zones of 35 mm and 26 mm, respectively, at 0.1 mg/mL within the study. Furthermore, compared with the synthesized derivative J1, the synthesized derivative J3 exhibited stronger cytotoxic activity against the MCF-7 cell line, with IC50 values of 123.8 and 160.3 µg/mL, respectively. Finally, on the basis of ADMET prediction data, the gastrointestinal absorption of all three molecules is expected to be low, and only derivatives J3 and J2 will comply with the proposed rules of Lipinski's rule.

Keywords
Amoxicillin, Drug resistance, Imine, MCF-7.

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Introduction

Drug resistance affects many diseases, but cancer and bacterial infections are especially prevalent [1]. These two disease categories (prokaryotes vs. eukaryotes) share cell-intrinsic resistance mechanisms despite their different cell types. Genetic alterations that involve the overexpression of drug efflux pumps, modification of drug targets, or inactivation of drugs enzymatically are the most common techniques [2]. Oncology gains are threatened by antimicrobial resistance (AMR), which makes infection-related cancer therapy consequences more difficult to control [3]. The indirect effects of anticancer treatment on AMR risk are widely documented; however, data on the direct effects of chemotherapeutic drugs on bacterial drug resistance are rare [4].

Antibiotics reduce cancer growth, increase apoptosis, and inhibit metastasis, and adjuvant antibiotics stimulate the immune system, fight cancer [5], improve the body, promote therapeutic efficacy, and prevent cancer from returning and spreading [6]. One potential antibiotic is amoxicillin, which has several biological functions. It is bacteriolytic and contains penicillin-class β-lactam antibiotics [7]. Amoxicillin has a broad spectrum of action, and greater blood concentrations come from better oral absorption than ampicillin, which fights bacteria [8]. Schiff base ligands of amoxicillin have been widely employed as bactericidal agents to treat bronchitis, tonsillitis, throat, ear, typhoid, pneumonia, and urinary tract infections [9, 10]. Recent studies have shown the effectiveness of β-lactams, namely, N-methylthio (A) and N-ethylthio (B). With this innovative class of drugs, apoptosis has been detected in breast, leukemia, and prostate cancer cell lines. Thus, medicinal chemistry benefits greatly from this family of molecules [11].

In this study, amoxicillin modification was used to synthesize three new imine derivatives, J1-J3, and these derivatives were characterized by FTIR. Biological activity against different bacterial strains was tested, and the cytotoxicity of the anti-breast cancer cell line MCF-7 was studied by an MTT assay.

Methodology

Synthesis of amoxicillin-imine compounds J1-J3

In accordance with the procedure of [12], novel imine compounds (J1-J3) were synthesized through the reaction of amoxicillin with different aldehyde derivatives. In a separate flask, 0.01 moles of 2,4-dihydroxy-3-propylbenzaldehyde, 3-ethyl-4-hydroxy-5-methylbenzaldehyde, and 2-(3-formyl-4-hydroxyphenyl)acetonitrile were dissolved in 15 mL of absolute ethanol, after which 1 drop of glacial acetic acid was added. A 4.19 g (0.01 mol) sample of amoxicillin was mixed with these solutions and refluxed for 2 h at 50 °C with continuous stirring. These 3 solutions formed yellow-to-yellowish-orange precipitates. After filtering, the precipitates were washed with absolute ethanol, dried, and collected. The derivative J1 is yellow, J2 is light yellowish-orange, and J3 is yellowish-orange.

2.3 Study of the antibacterial activity of synthesized derivatives J1-J3

Different bacterial strains, such as Bacillus subtilis and Streptococcus pyogenes, were cultured on Mueller–Hinton agar plates using sterile loops and streaking procedures, commencing with the broth culture. A separate well was formed in the agar media. The synthesized derivatives (J1-J3) (0.1, 0.001, and 0.00001 mg/mL) were added to each well, facilitating effective absorption. The container was securely sealed and incubated overnight at 37 °C and evaluated the following day. [13].

3 Molecule Library Preparation

ChemDraw Ultra 12.0 was employed to create the 3D structures of the newly synthesized compounds J1-J3, followed by energy minimization. The structures were preoptimized by employing the semiempirical AM1 method in HyperChem 8.08. All the measured ligand vibrational frequencies are positive, indicating stability. The optimized structures were consolidated into a single database with MOE software (2022) to evaluate ligand affinity [14].

The protein is prepared by removing water molecules and adding hydrogen atoms in the active region to facilitate hydrogen bonding with ligands [15]. So, this research studied the interaction between ligands and the target 6IIO protein [17]. Molecular docking and scoring were performed using Molecular Operating Environment (MOE, 2019) software. [16].

The docking target was PDB ID 6IIO, a protein structure with a well-characterized binding pocket that has been used in computational research for ligand binding assessment. This protein was used to assess the interaction patterns, binding affinity, and structural compatibility of freshly synthesized imine-amoxicillin derivatives. Using a previously documented docking target allows comparison of findings with those of comparable computational studies and provides preliminary insight into the biological behavior of synthesized drugs. The serine/threonine protein kinase GSK-3β controls several physiological processes, including cell proliferation, death, differentiation, and signal transduction pathways. GSK-3β is a possible target for the development of anticancer medications because of its association with breast cancer progression. Owing to its well-resolved crystal structure and previous computational screening efforts, PDB 6IIO was selected for this study. Evaluation of the binding affinity of the synthesized imine-amoxicillin derivatives for this target provides preliminary evidence of their potential anticancer action and molecular links to MCF-7 cell cytotoxicity.

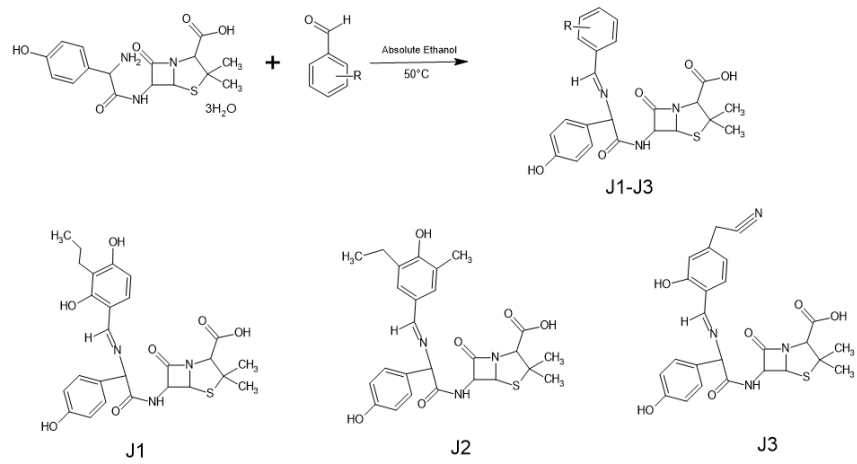
Cytotoxicity activity of synthesized derivatives against MCF-7 cells

MCF-7 breast cancer cells were seeded in 96-well plates at 1 × 10^4 cells/well in 200 µL of growth media. They were incubated overnight at 37 °C in a humidified environment with 5% CO_2. Serial quantities of synthesized derivatives (0, 20, 40, 80, 160, and 320 µg/mL) were applied to cells after attachment. To test for formazan crystal formation, 10 µL of MTT solution was added to each well after 24 hours of treatment.

The supernatant was discarded, and 100 µL of DMSO was added to dissolve the crystals. An ELISA microplate reader was used to measure the absorbance at 575 nm. Cell viability was compared to that of the untreated controls. Three separate experiments were used to calculate the IC_{50} values from the concentration–response curves using nonlinear regression analysis in GraphPad Prism software. The results are presented as the mean ± SD [17].

Results and Discussion

Different new imine-amoxicillin compounds, J1-J3, were successfully synthesized by using amoxicillin trihydrate as a drug, which was modified by reacting with three aromatic aldehyde derivatives under absolute ethanol as a solvent and one drop of glacial acetic acid as a catalyst [18]. The reaction mixtures produced yellow to yellowish-orange precipitates, indicating the formation of new conjugated imine products. The use of glacial acetic acid as a mild catalyst promoted the formation of the azomethine linkage while maintaining relatively soft reaction conditions [19].



Scheme 1. Routes of synthesized derivatives J1-J3.

Characterization

FTIR analysis was used to confirm the successful synthesis of derivatives J1-J3, which revealed different bands for the active groups. In these Schiff base reactions, a new band corresponding to the imine group C=N and the disappearance of the C-H aldehyde at 2700 cm-1 and the carbonyl aldehyde C=O at 1730 cm-1 appeared, in addition to two bands at 3200–3300 cm-1 for the primary amine of the aromatic amine, which is used as a drug [20].

The imine derivatives of J1, J2 and J3 appeared at 1643, 1620, and 1644, respectively, while the C-H aliphatic chain at 2968, 2975, and 2908 and the hydroxyl groups O-H appeared at 3396, 3515, and 3282, respectively, as shown in Figs. 1-3.

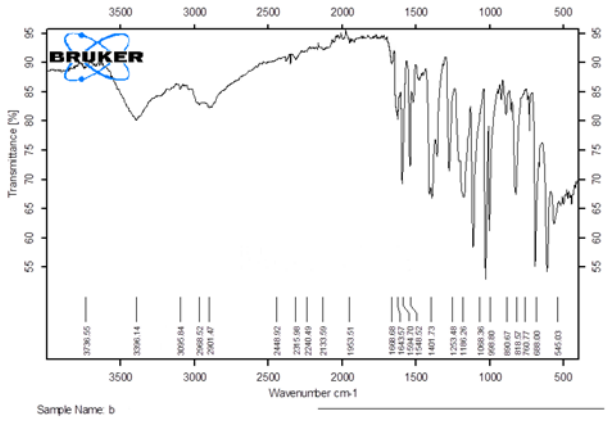


Figure 1. FTIR spectrum of the synthesized imine derivative J1.

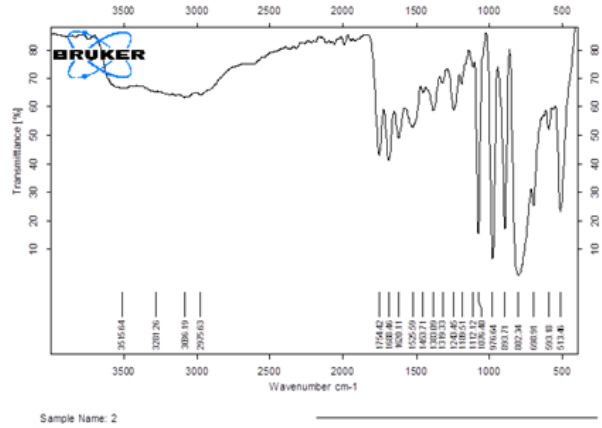


Figure 2. FTIR spectrum of the synthesized imine derivative J2.

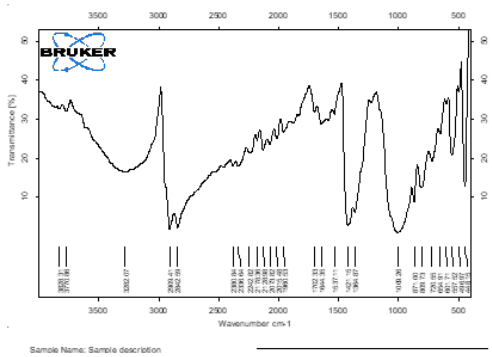


Figure 3. FTIR spectrum of the synthesized imine derivative J3.

Molecular Docking

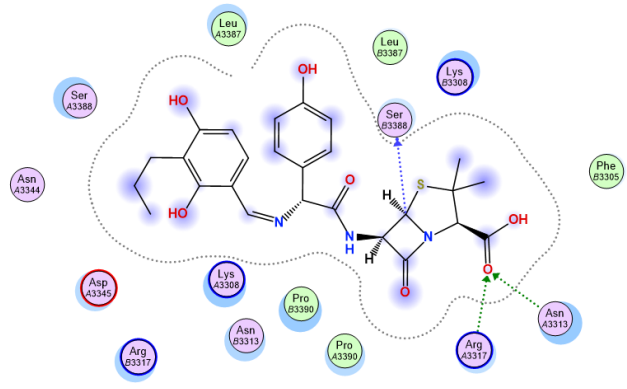
As shown in Table 1, the molecular docking results of imine-synthesized derivatives J1-J3 against the target protein (PDB 6IIO) suggest that derivative J2 obtained the best docking score of -8.18972 kcal/mol, followed closely by derivative J3, with a score of -8.1703 kcal/mol. Derivative J1, however, had a docking score of -7.83371 kcal/mol than the two previously synthesized imine derivatives did. In addition, compared with the reference ligand, all three compounds presented significantly improved docking scores, which were -3.7740 kcal/mol.

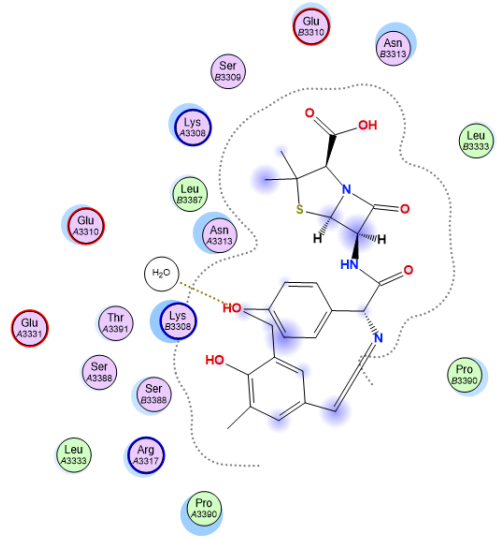
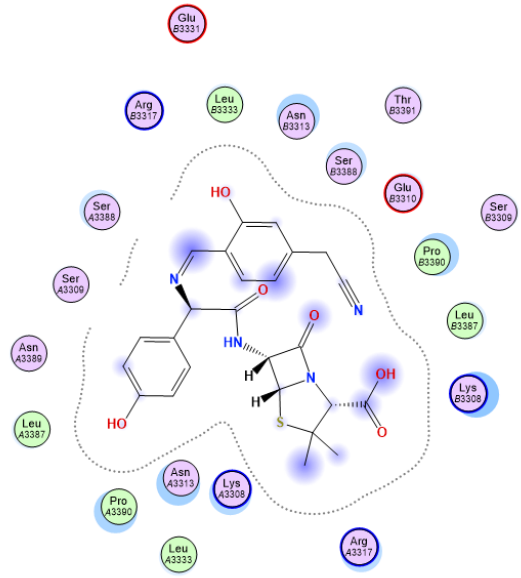
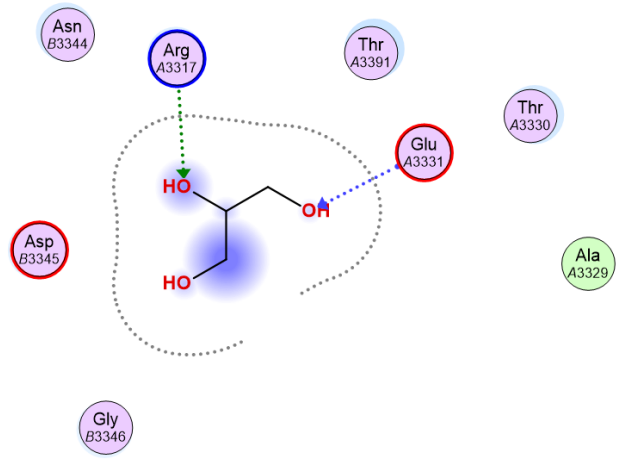
Table 1. Molecular docking results of synthesized derivatives and the 6IIO target protein.

Compound No.	mol. smiles	S	rmsd_refine
J1	OC(=O)C1N2C(SC1(C)C)C(NC(=O)C(\N=C\c1ccc(O)c(CCC)c1O)c1ccc(O)cc1)C2=O	-7.83371	1.217952
J2	CC1(C)SC2N(C(=O)C2NC(=O)C(\N=C\c2cc(CC)c(O)c(C)c2)c2ccc(O)cc2)C1C(O)=O	-8.18972	2.36675
J3	OC(=O)C1N2C(SC1(C)C)C(NC(=O)C(\N=C\c1ccc(CC#N)cc1O)c1ccc(O)cc1)C2=O	-8.1703	2.466202
Reference	OCC(O)CO,1,1	-3.7740	28.2218

The improved docking of the imine derivative J2 can be due to the different substituted groups, such as ethyl, methyl, and hydroxyl groups, in the aromatic ring, which increase the number of hydrophobic interactions and increase the degree of hydrogen bonding activity with the active site of the 6IIO target protein. The activity of the other derivative, J3, is strong because of the presence of a nitrile group, which creates additional polar interactions with the 6IIO target protein. In comparison, the synthesized derivative J1 has high activity and the lowest docking score, which is due to the presence of dihydroxy and propyl groups on the aromatic ring.

Table 2. Molecular docking interactions between synthesized derivatives and the 6IIO target protein.

Compound No.	Interaction
J1	

J2	
J3	
References	

Interestingly, the docking results did not match the experimental biological findings, and the synthesized derivative J3 had better antibacterial and cytotoxic activities against MCF-7 cells than the derivative J2, which had the greatest docking score against the target protein. Such discrepancies are commonly observed in drug discovery studies because docking simulations examine ligand–protein interactions under idealized and static settings. However, their solubility, membrane permeability, metabolic and chemical stability, cellular absorption, intracellular accumulation, and interactions with various biological targets affect their biological activity. Compared with derivative J1, the nitrile-containing derivative J3 had better anticipated water solubility and similar physicochemical attributes to derivative J2, which may have increased biological accessibility and experimental effectiveness. Thus, compared with biological potency assessments, docking scores are beneficial prognostic markers.

Anti-Breast cancer MCF-7

There was a significant concentration-dependent decrease in the viability of the MCF-7 breast cancer cells when 20–320 µg/mL synthesized imine derivatives were used, indicating that these derivatives exhibited concentration-dependent antiproliferative effects. All of the synthesized derivatives, J1 and J3, were found to be cytotoxic to the MCF-7 cell line; however, derivative J3 had a lower IC50 value (123.8 µg/mL) than derivative J1 (160.3 µg/mL). These findings suggest that, compared with J1, derivative J3 requires less than half the concentration; therefore, derivative J3 exhibited greater antiproliferative activity under the present experimental conditions, as shown in Figs. 4-7. The data are presented as the mean ± SD of three independent experiments (n = 3).

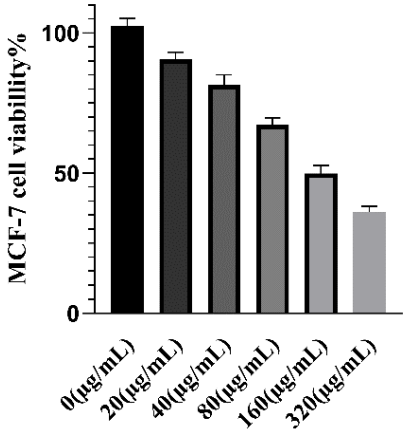


Figure 4. Effect of the synthesized imine derivative J1 on MCF-7 cell viability.

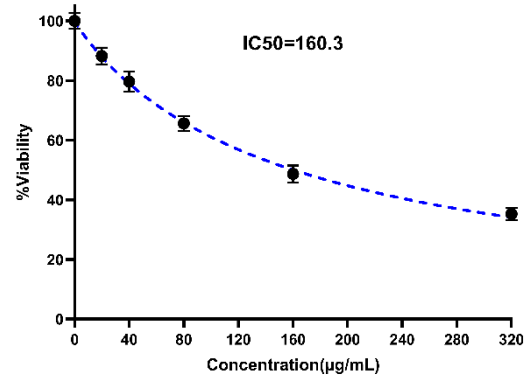


Figure 5. Dose–response curve of MCF-7 cell viability with synthesized imine derivative J1.

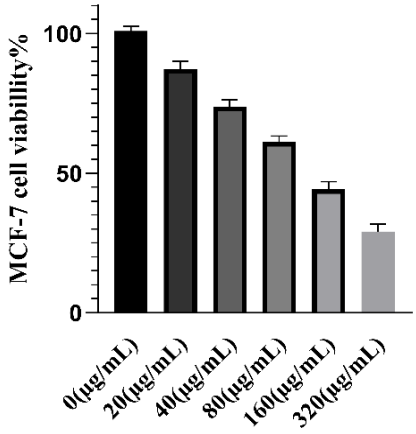


Figure 6. Effect of the synthesized imine derivative J3 on MCF-7 cell viability.

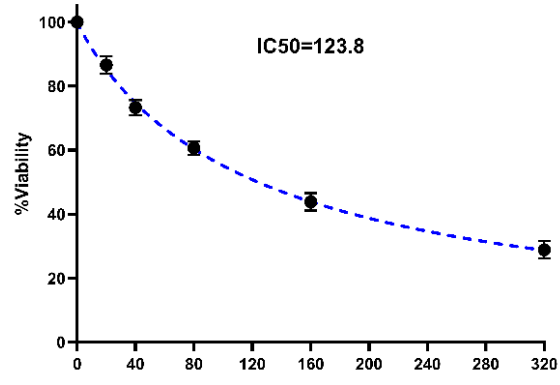
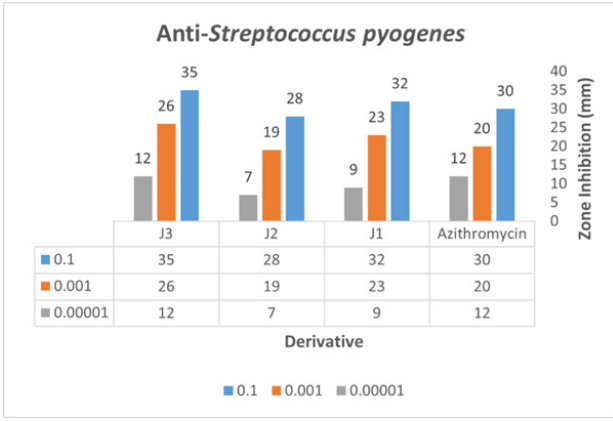


Figure 7. Dose–response curve of MCF-7 cell viability with synthesized imine derivative J3.

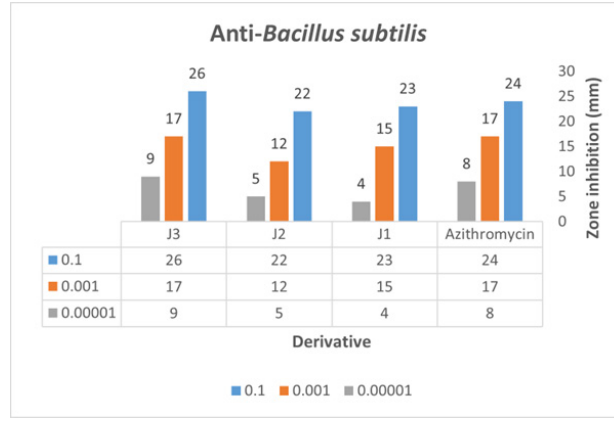
Biological activity

The overall results suggest that synthesized imine derivatives J1-J3 have antibacterial properties, with derivative J3 exhibiting maximum activity against different bacteria. The greater potency of derivative J3 (35 and 29) against S. pyogenes than against B. subtilis could be due to the presence of the nitrile moiety, which would facilitate polar interactions with yet-to-be-identified bacterial receptors and thus enhance the biological response. Compared with B. subtilis, the derivatives J2 were 28 mm and 22 mm long, whereas azithromycin, as a reference drug, showed biological activity of 30 and 24; however, the activity of derivative J3 was greater against all the bacteria that were used. The stronger activity demonstrated against S. pyogenes than against B. subtilis suggests that the antibacterial activity may be contingent upon the structure of the imine as well as the susceptibility of the bacteria involved. These data support the notion that imine derivatives may represent a class of biologically active antibacterial candidates; however, additional testing to determine MICs and screen a larger number of bacteria would be necessary to establish their utility for therapeutic use, as shown in Figs. 8 and 9.



	J3	J2	J1	Azithromycin
0.1	35	28	32	30
0.001	26	19	23	20
0.00001	12	7	9	12

Figure 8. Antibacterial activity of synthesized derivatives J1-J3 against S. pyogenes.



	J3	J2	J1	Azithromycin
0.1	26	22	23	24
0.001	17	12	15	17
0.00001	9	5	4	8

Figure 9. Antibacterial activity of synthesized derivatives J1-J3 against Bacillus subtilis.

Drug-likeness properties

The in silico ADMET of synthesized imine-amoxicillin derivatives (J1-J3) resulted in all three having very high molecular weights between 508.55 and 527.59 g/mol. J1 had the highest weight of these compounds at 527.59 (TPSA = 185.06 Å²; 9 rotatable bonds, 8 hydrogen-bond acceptors, and 5 hydrogen-bond donors). The synthesized derivative J2 had a molecular weight of 511.59 (TPSA = 164.83 Å²; 8 rotatable bonds, 7 hydrogen-bond acceptors, 4 hydrogen-bond donors), and the derivative J3 had a molecular weight of 508.55 (TPSA = 188.62 Å²; 8 rotatable bonds, 8 hydrogen-bond acceptors, 4 hydrogen-bond donors).

An in silico evaluation revealed that the lipophilicity of derivative J2 was the highest, with an XLOGP3 value of 3.48, whereas that of derivative J1 was 3.30, whereas that of J3 was the lowest (1.97). Water solubility predictions: derivative J3 showed the best solubility and ESOL profile, with Log S = -3.95, and was classified as soluble, whereas derivative J1 has Log S = -4.84 and derivative J2 has Log S = -4.92, which were classified as having moderate solubility. However, on the basis of the Ali model for solubility, synthesized derivatives J1 and J2 were classified as having poor solubility, whereas J3 was classified as having moderate solubility.

The pharmacokinetic prediction revealed that all three newly synthesized derivatives had low gastrointestinal absorption. None of the compounds were predicted to penetrate the blood–brain barrier, but all the predicted skin permeabilities were low, with log Kps values of -7.18, -6.95 and -8.00 cm/s for synthesized derivatives J1, J2 and J3, respectively. Drug likeness evaluation demonstrated that all the compounds were compliant with Lipinski's rule, with only one violation due to a molecular weight >500 g/mol. However, the Ghose, Veber, Egan, Muegge, and lead-likeness filters were not entirely satisfactory, primarily because of their high molecular weights, high TPSAs, and high molecular flexibility. All derivatives had zero PAINS alerts, with one Brenk alert attributed to the imine group, and moderate synthetic accessibility values ranging from 5.05 to 5.33.

Discussion

The formation of yellow to yellow–orange precipitates from an amoxicillin and aromatic aldehyde reaction in ethanol supports the successful synthesis of new imine-amoxicillin derivatives J1-J3. After condensation, the resulting conjugated azomethine system produced a color change. Glacial acetic acid acted as a mild catalyst, facilitating imine formation without exposing the β-lactam to harsh acids or bases that could degrade the β-lactam antibiotics.

FTIR analyses provided strong evidence for the formation of imine derivatives, and new C=N bonds of the azomethine group were detected at 1643, 1620, and 1644 cm-1 for derivatives J1, J2, and J3, respectively, thus confirming the forma-

tion of Schiff bases.

In a molecular docking experiment with the target protein 6IIO, compared with the reference compound, all synthesized derivatives showed better predicted binding affinity to the target protein. Derivative J2 exhibited the best docking score at -8.18972 kcal/mol, followed closely by derivative J3 at -8.1703 kcal/mol for each compound. In comparison, derivative J1 has a slightly lower docking score of -7.83371 kcal/mol. This finding indicates that modification of amoxicillin via imine has created more favorable theoretical interactions with the target protein when these compounds are being examined. The greater than expected performance of derivative J2 compared with the other two compounds could be due to the presence of ethyl, methyl and hydroxyl groups on the aromatic ring of derivative J2, which would create additional hydrophobic interactions and hydrogen bond interactions in the active site of the target protein.

Analysis of the RMSD refinement values reinforced the validity of the docking poses; derivative J1 exhibited the lowest RMSD at 1.217952, indicating a stable conformation when bound to the target protein. The RMSD values of derivative J2 at 2.36675 and derivative J3 at 2.466202 are considered to be reasonable, suggesting moderate stability for these two derivatives when bound to the target protein 6IIO.

The results of the cytotoxicity studies revealed that the degree of toxicity exhibited by the synthesized derivatives increased with increasing concentration. Compared with derivative J1, derivative J3 appeared to have relatively potent cytotoxicity at an IC50 of 123.8 µg/mL, which had an IC50 of 160.3 µg/mL; therefore, the lower IC50 value of derivative J3 indicates that it is necessary to use less than half the concentration of this compound to exert a 50% inhibitory effect on MCF-7 cell viability. One possible reason for the enhanced activity of the derivative J3 is the influence of the nitrile-substituted aromatic moieties on the polarity, cellular interaction, and binding properties of this synthesized derivative; however, it would be necessary to conduct additional mechanistic experiments, such as apoptosis, ROS generation, and cell cycle analysis, to determine the precise mechanisms of action for the anticancer properties associated with these derivatives [21-23].

The synthesized compounds showed concentration-dependent cytotoxic effects against MCF-7 breast cancer cells; however, these results are tentative since only one cancer cell line was tested. The present findings suggest antiproliferative activity but not anti-breast cancer effectiveness. To understand the mechanisms of these drugs, apoptosis induction, cell cycle arrest analysis, ROS production, and caspase activation studies are needed.

Antibacterial testing of the synthesized imine derivatives revealed the ability of these compounds to demonstrate measurable antimicrobial activity against all the bacterial isolates tested. Derivative J3 exhibited the largest zone of inhibition of all the test compounds against the Streptococcus pyogenes and Bacillus subtilis isolates, suggesting that the architectural features of derivative J3 contribute to the enhanced antibacterial effects of this derivative. Specifically, at a concentration of 0.1 mg/mL, derivative J3 produced a zone of inhibition of 35 mm against S. pyogenes, thereby exceeding the zone of inhibition of 30 mm for reference azithromycin, and exhibited a zone of inhibition of 26 mm against B. subtilis compared with 24 mm for the reference drug azithromycin; therefore, these results suggest that the nitrile-containing imine derivative confers enhanced antimicrobial activity through its increased affinity for target bacteria [24-26].

Again well diffusion experiments revealed antibacterial activity for the synthesized compounds; however, inhibition zone measurements cannot quantify potency. Thus, to further measure the antibacterial effectiveness of these compounds, the MIC and MBC must be determined. Future research will use MIC and MBC tests to determine the bacteriostatic and bactericidal capabilities of the most active derivatives.

Overall, the results of both biological and docking studies indicate that the synthesized imine form of amoxicillin may improve its drug profile. The derivative J3 has the most promising antibacterial and anticancer activity, while the derivative J2 has the highest docking score, representing two extremes with respect to the differences between computational and biological activities. The differences between these two measures, which could be attributed to factors such as solubility, stability, or cellular uptake, necessitate further study involving comparing the imine derivatives to amoxicillin using MIC and MBC assays and standard antibiotics; cytotoxicity tests using normal cell lines; and molecular dynamics analyses to establish better support for the biological activity of these imine–amoxicillin hybrids.

This study has several limitations. No normal cell line was used for selectivity testing in the anticancer study of MCF-7 breast cancer cells. The mechanism of the reported cytotoxic action was not examined by apoptosis tests, cell cycle analysis, ROS measurements, or caspase activation investigations. Therefore, the anticancer results should be considered preliminary data requiring biological confirmation and mechanistic research.

There was no normal cell line in this study; hence, the selectivity index (SI) could not be calculated. Further research is needed to determine the toxicity of these chemicals to healthy cells and their therapeutic potential.

Conclusion

Amoxicillin imine hybridization is a viable way to synthesize imine-amoxicillin derivatives with enhanced therapeutic activity. The preparation of the hybrid derivative J1 through derivative J3 was accomplished under mild ethanolic conditions and confirmed by color changes and FTIR spectroscopy, with the detection of azomethine bands as evidence of imine formation. Furthermore, molecular docking studies revealed that the affinity of the hybrids was generally greater than that of amoxicillin for the 6IIO target, while biological testing indicated that derivative J3 had the best potential because it had the highest antibacterial activity and the lowest IC_{50} value

against MCF-7 cells, and it appears that the presence of an aromatic fragment that contains a nitrile increased the activity of the hybrids. That said, this work is preliminary in nature, as antibacterial assessment was limited to measuring inhibition zones, cytotoxicity was limited to cancer cell lines, and ADMET predictions indicated low gastrointestinal absorption. Thus, further studies need to include the MIC, MBC, cytotoxicity to noncancerous cells, apoptosis, ROS generation, cell cycle activity, stability at 37 °C, and molecular dynamics before therapeutic claims can be made. Future studies will also include broader antimicrobial evaluations and additional anticancer mechanistic assays of derivative J3. On the basis of these data, derivative J3 represents a useful investigational lead but requires further optimization of pharmacokinetic properties, assessment of safety, and clarification of the precise mechanism at the molecular level under related physiological and pathological experimental conditions.

Author Declarations

Acknowledgments

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Author Contributions

B.H.B. contributed to conceptualization, methodology, investigation, data collection, literature review, and preparation of the original manuscript draft. N.H.B. contributed to validation, manuscript review, and editing. Z.A.A. contributed to formal analysis, visualization, and interpretation of the results. Z.T.S. contributed to resources, project administration, and technical support.

All authors critically revised the manuscript, approved the final version, and agreed to be accountable for all aspects of the work.

Data Availability Statement

Data supporting the findings of this study are available from the corresponding author upon reasonable request.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

Ethics Approval and Consent to Participate

Not applicable. This study did not involve human participants, animal experiments, human tissues, or identifiable personal data requiring ethical approval or informed consent.

Consent for Publication

Not applicable.

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