Archives of Pharmaceutical Sciences and Research E-ISSN 0975-2633 | PRINT ISSN 0975-5284
Vol 16 Issue 1 001 – 007 March 2026 Research Article

SYNTHESIS AND STRUCTURAL CHARACTERIZATION OF AMPICILLIN-DERIVED SCHIFF BASES WITH ENHANCED BIOLOGICAL POTENTIAL

Mr. Rajashekhar N[1], Ms. Mounashree U[2], Ms. Nanditha B R[3].

1. Assistant Professor, Department of Pharmacology, SCS Institute of Pharmaceutical Sciences, Hospete, Sanklapur, Karnataka, India.
2. Assistant Professor, Department of Pharmacology, Rajeev College of Pharmacy, Hassan, Karnataka, India.
3. Assistant Professor, Department of Pharmaceutical Chemistry, Rajeev College of Pharmacy, Hassan, Karnataka, India.

ABSTRACT

The growing challenge of antimicrobial resistance necessitates the structural modification of existing antibiotics to improve their efficacy. Ampicillin, a widely used semi-synthetic β-lactam antibiotic, exhibits broad-spectrum activity but is vulnerable to β-lactamase degradation. Schiff base formation offers a promising approach to enhance its stability and antimicrobial potential. The present study focuses on the synthesis, characterization, and biological evaluation of Schiff base derivatives of ampicillin using selected ketones. Ampicillin was reacted with acetophenone, benzoin, and anthrone under microwave-assisted conditions in methanol with concentrated hydrochloric acid as a catalyst, yielding three derivatives: APAC, APB, and APA. Product formation was monitored using TLC. The synthesized compounds were structurally characterized through FT-IR, ^{1}H-NMR, mass spectroscopy, and melting point analysis. FT-IR spectra confirmed the presence of characteristic azomethine (C=N), carbonyl (C=O), hydroxyl, and amide groups. ^{1}H-NMR data validated the proton environment of APAC, while the mass spectrum of APA showed a molecular ion peak at m/z 525, consistent with its molecular formula. Biological screening of selected derivatives demonstrated improved antimicrobial activity compared to ampicillin. Physicochemical parameters, including C log P, drug-likeness, and drug score, supported the compounds' suitability as drug candidates. Overall, the synthesized Schiff bases showed promising potential as enhanced antibacterial agents.

Keywords: Ampicillin, Antibacterial activity, FT-IR, ^{1}H-NMR, Ketone derivatives, Mass spectrometry, Schiff bases.

INTRODUCTION

Humankind has been affected by infectious diseases since ancient times, long before the microbial origin of infections was understood. Early therapeutic approaches relied on empirical remedies such as plant extracts, animal-derived preparations, and fermented materials, which often yielded inconsistent therapeutic outcomes[1]. A major turning point occurred with the discovery of microorganisms and the establishment of germ theory, which laid the foundation for rational antimicrobial therapy[1].

Antibiotics are microbial metabolites or their synthetic analogues that revolutionized infectious-disease management by selectively inhibiting or killing pathogens while causing minimal host toxicity[1]. However, their widespread and sometimes irrational use accelerated the emergence of resistant and multidrug-resistant microorganisms, posing a significant global health challenge[2].

Although several natural antibiotics remain effective, many have required structural modification to improve potency, stability, pharmacokinetics, and safety[3]. Medicinal chemistry efforts have yielded numerous semisynthetic antibiotics with improved clinical profiles[3]. However, the rate of discovery of new antibacterial agents has slowed considerably due to scientific and economic constraints, even as antimicrobial resistance continues to increase sharply[4]. This situation has intensified research into developing novel or structurally modified antibacterial agents[4].

Ampicillin, an aminopenicillin belonging to the β-lactam class, acts by inhibiting transpeptidase enzymes involved in bacterial cell-wall synthesis, resulting in rapid bacterial death[5]. Compared with natural penicillin, ampicillin exhibits enhanced acid stability and broader antimicrobial activity owing to the presence of its electron-withdrawing amino group[5].

Nonetheless, it is susceptible to hydrolysis by β-lactamase enzymes, which significantly reduces

its activity against resistant strains, especially *Staphylococcus* species[6]. Semisynthetic derivatives such as amoxicillin, bacampicillin, hetacillin, and talampicillin have been developed to enhance activity and bioavailability, but resistance remains a major therapeutic limitation[6].

Chemical modification of antibiotics has emerged as a promising strategy for restoring or improving antibacterial potency. One such approach is the formation of Schiff bases, which are condensation products of primary amines with aldehydes or ketones, characterized by the azomethine (–C=N–) functional group[7]. Schiff bases and their metal complexes exhibit a wide spectrum of biological activities, including antibacterial, antifungal, antiviral, antimalarial, anti-inflammatory, and anticancer effects[7,8].

Incorporating Schiff base moieties into β-lactam antibiotics may enhance lipophilicity, facilitate membrane penetration, improve drug–target interactions, and potentially overcome resistance mechanisms[8,9]. Previous studies on Schiff-base-modified penicillins and cephalosporins have reported improved stability and antibacterial profiles[10]. Therefore, synthesizing Schiff base derivatives of ampicillin using selected ketones may yield novel analogues with enhanced physicochemical and antimicrobial properties[11].

MATERIALS AND METHODS

Chemicals and Reagents

Ampicillin, Acetophenone, Benzoin, Anthrone, Methanol, Concentrated HCl, and other analytical reagents were utilized. All chemicals, of analytical grade, were obtained from S.D. Fine Chem. Ltd., Mumbai[12].

Synthesis of Schiff Base Derivatives

Ampicillin (2 mmol) was dissolved in methanol. Equimolar ketone (acetophenone, benzoin or anthrone) was added, followed by two drops of concentrated hydrochloric acid. The mixture was subjected to microwave irradiation for 10–15 cycles at intermittent intervals. The reaction mixture was then poured into ice-cold water to precipitate the product. The solid obtained was filtered, washed and dried [13,14].

The synthesized compounds were designated as:

1. **APAC:** Ampicillin–acetophenone Schiff base
2. **APB:** Ampicillin–benzoin Schiff base
3. **APA:** Ampicillin–anthrone Schiff base

TLC Analysis

Reaction completion was monitored by thin-layer chromatography using a mobile phase of ethyl acetate: toluene (5:1). Spots were visualized under UV light[14,15].

Characterization

1. **Fourier Transform Infrared Spectroscopy (FT-IR):** Used to confirm azomethine (C=N), carbonyl, hydroxyl, and amide functionalities[14,16].
2. **Proton Nuclear Magnetic Resonance (^{1}H-NMR):** Performed for APAC derivative to determine proton environments[14,16,17].
3. **Mass Spectrometry:** APA derivative was subjected to mass analysis to determine the molecular ion peak[16,17].
4. **Melting Point:** Determined using the capillary method to assess purity[14,16].

Physicochemical Property Evaluation

C log P, drug-likeness, and drug score values were calculated using computational prediction tools[17,18].

Antimicrobial Screening

Synthesized derivatives were evaluated using the agar diffusion method against standard bacterial strains, and activity was compared with that of standard ampicillin[15,16,17].

RESULTS

Synthesis

All three Schiff base derivatives were successfully synthesized using microwave-assisted condensation. The products were obtained as crystalline solids with satisfactory yields.

Table 1: Synthesis of Schiff base derivatives of Ampicillin with various ketones

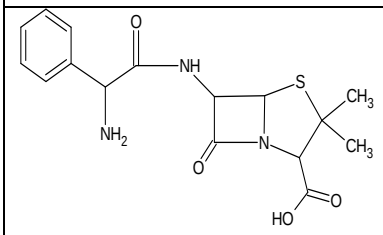
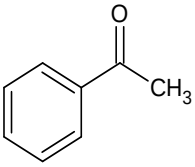
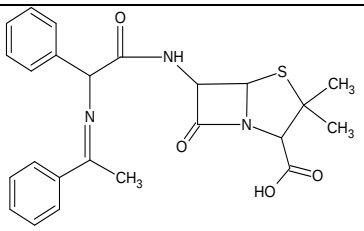
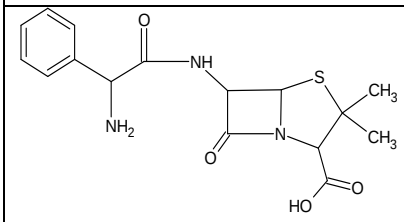
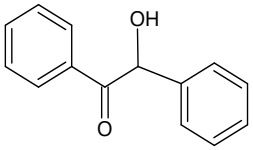
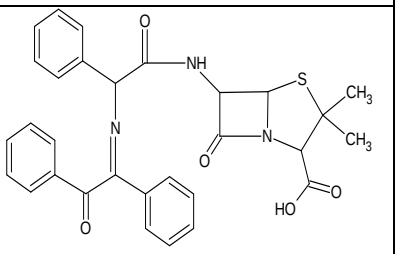
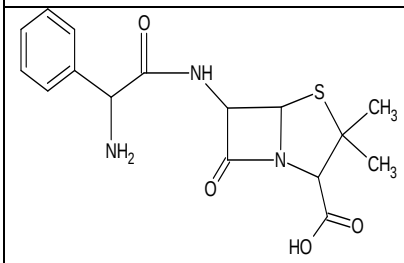
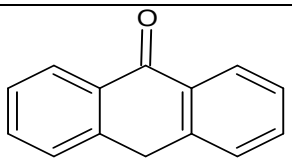
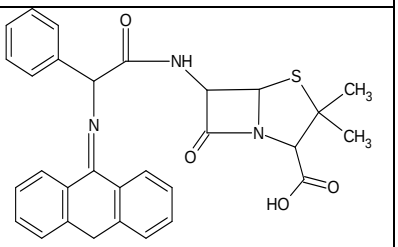
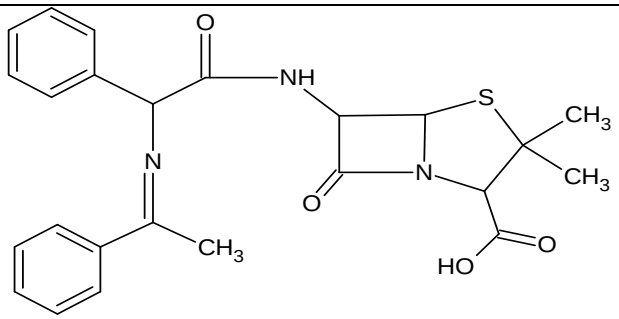
Starting material	Ketones	Final product
 Ampicillin	 Acetophenone	 Schiff base derivative
 Ampicillin	 Benzoin	 Schiff base derivative
 Ampicillin	 Anthrone	 Schiff base derivative

Table 2: Spectroscopical data of APAC

Structure:	
Physical state	Yellow solid
Melting point	126°C
^{1}H-NMR Analysis	
Aromatic protons	δ 7.4–8.6

C-H proton	δ 4.8
Methyl protons	δ 1.4

Table 3: Spectroscopical data of APB

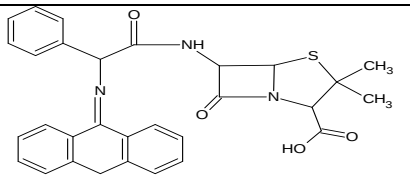
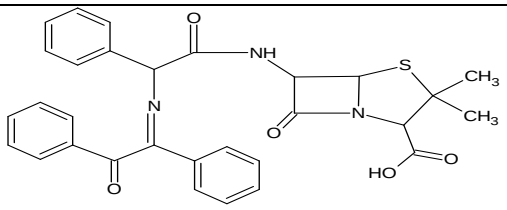
Structure:	
Physical state	Yellow solid
Melting point	178°C
FT-IR Analysis	
Stretching of azomethine (C=N)	1474.20 cm^{-1}
NH and OH stretching	Between 3300–3410 cm^{-1}
Carbonyl (C=O) stretching	Near 1670 cm^{-1}
C–S–C stretching	Between 1000–1100 cm^{-1}
MASS SPECTRA	
Molecular ion peak	At m/z 525

Table 4: Spectroscopical data of APA

Structure:	
Physical state	Yellow solid
Melting point	170°C
FT-IR Analysis	
Stretching of azomethine (C=N)	1470 cm^{-1}
NH and OH stretching	Between 3300–3400 cm^{-1}

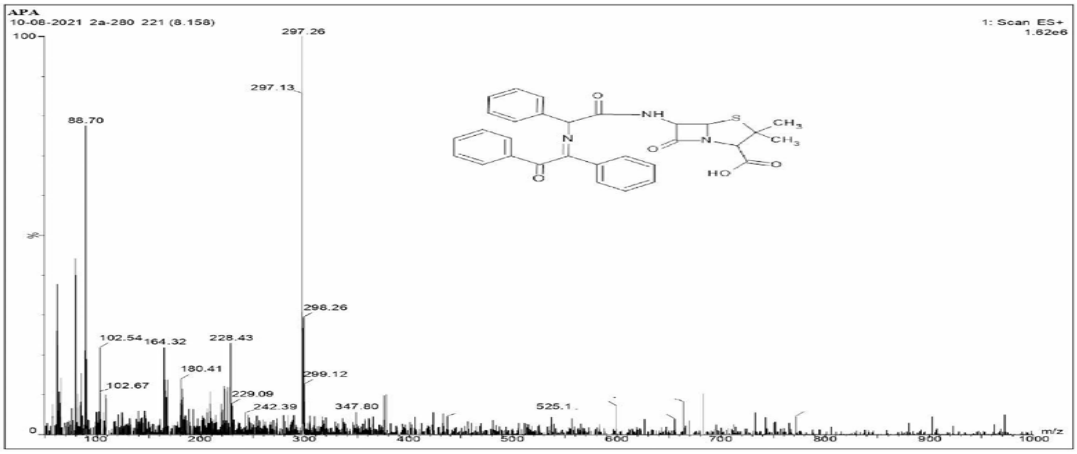


Figure 1: H-NMR spectra of APAC

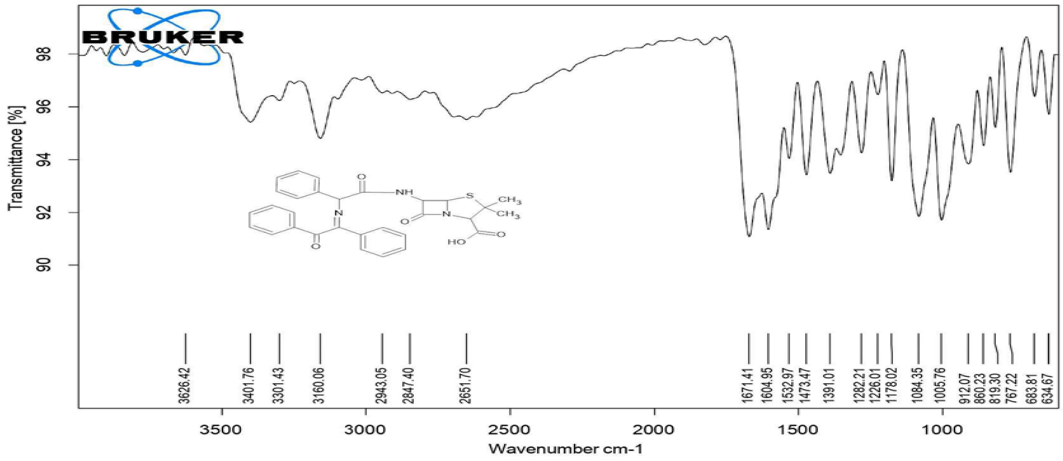


Figure 2: FT-IR Spectra of APB

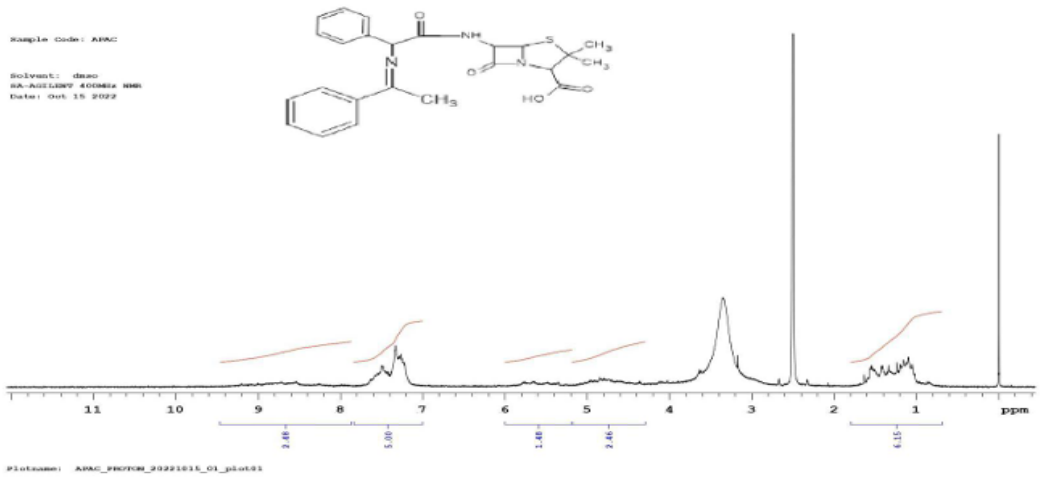


Figure 3: FT-IR Spectra of APA

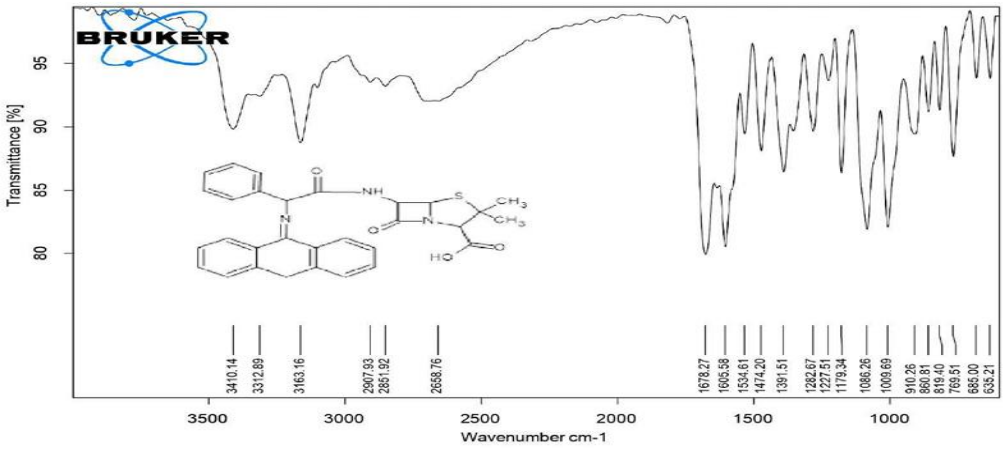


Figure 4: Mass Spectra of APB

A molecular ion peak at **m/z 525** confirmed the molecular weight corresponding to **$C_{30}H_{28}N_3O_4S$**, supporting the expected structure

Physicochemical Properties

All derivatives exhibited improved drug-likeness scores compared to pure ampicillin. Increased C log P values suggested enhanced lipophilicity.

Antimicrobial Activity

All three derivatives demonstrated notable activity against test organisms. The zone of inhibition was greater than that of pure ampicillin, especially for the APA derivative. This indicates that Schiff base formation improves antimicrobial potential.

Figure 5: Antimicrobial activity of APA

DISCUSSION

The microwave-assisted synthesis of ampicillin Schiff base derivatives, supported by FT-IR, NMR, and mass spectrometric confirmation of azomethine formation, directly addresses the study's aim of generating and characterizing structurally validated derivatives of the parent drug. The observed changes in lipophilicity, as reflected by calculated C log P values, indicate that Schiff base modification can modulate key physicochemical properties that influence membrane interaction and may contribute to altered antimicrobial performance. While these trends are suggestive, they highlight the need for broader evaluation to establish definitive structure–activity relationships.

Among the synthesized compounds, APA exhibited comparatively higher stability and more pronounced antimicrobial activity under the experimental conditions. This finding demonstrates that specific Schiff base modifications can influence biological response, adding to the existing body of knowledge on β-lactam structural optimization. The results therefore align with the study's objective of assessing whether Schiff base formation can serve as a viable approach to enhance the functional profile of ampicillin.

Overall, the study provides evidence that Schiff base derivatization represents a promising

strategy for modulating both the physicochemical and biological characteristics of ampicillin. These insights contribute to ongoing efforts in antibiotic modification and may inform future research aimed at improving the therapeutic performance of β-lactam derivatives through rational structural design.

CONCLUSION

Three Schiff base derivatives of ampicillin were successfully synthesized and structurally validated using FT-IR, ^{1}H-NMR and mass spectrometry, fulfilling the study's objective of generating and confirming modified analogues of the parent drug. The observed enhancement in antimicrobial activity relative to ampicillin indicates that Schiff base formation can influence the biological performance of β-lactam antibiotics. These findings contribute to existing knowledge by demonstrating that targeted modification at the amine site of ampicillin can yield derivatives with altered activity profiles, thereby supporting the broader concept of structural tailoring to overcome diminishing antibiotic efficacy. In the context of rising antimicrobial resistance, the study provides a preliminary but meaningful indication that Schiff base derivatization may serve as a viable strategy for identifying new antibacterial leads worthy of further optimization.

ACKNOWLEDGEMENT

The authors express their gratitude to the Department of Pharmaceutical Chemistry and laboratory staff for providing necessary support and instrumentation facilities.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

[1]. Victoria F.R., William Z.S., Lemke T., Williams D.A.; Foye's Principles of Medicinal Chemistry, 6th Ed.; Lippincott Williams & Wilkins, Philadelphia, 2010, 1028–1030.
[2]. Kadam S.S., Mahadik K.R., Bothara K.G.; Principles of Medicinal Chemistry, Vol. 1, 1st Ed.; Nirali Prakashan, Pune, 1995, 67–74.
[3]. da Silva C.M., da Silva D.L., Modolo L.V. et al.; J. Adv. Res., 2011; 2, 1–8.
[4]. Hesterkamp T.; Drug Discov. Today, 2006; 11(14–15), 667–672.
[5]. Rang H.P., Dale M.M., Ritter J.M.; Pharmacology; 5th Ed.; Churchill Livingstone, London, 2003, 646–650.
[6]. Bush K.; Clin. Microbiol. Rev., 2018; 31(4), 1–28.
[7]. Pandeya S.N., Sriram D., Nath G. et al.; Eur. J. Med. Chem., 1999; 34(9), 703–713.
[8]. Taggi A.E., Hafez A.M., Wack H.; J. Am. Chem. Soc., 2002; 124, 6626–6637.
[9]. Chohan Z.H., Shad H.A.; Appl. Organomet. Chem., 2015; 29(11), 759–766.
[10]. Al-Azzawi A.M.H.; J. Chem. Pharm. Res., 2015; 7(3), 758–765.
[11]. Garg M., Kumar S.; Int. J. Pharm. Sci. Res., 2012; 3(5), 1427–1434.
[12]. S.D. Fine Chem. Ltd.; Mumbai, India; Product Catalogue, 2022.
[13]. Mudhafar M.J. et al.; Int. J. Pharm. Sci., 2016; 8(5), 113–116.
[14]. Alias M., Kassum H., Shakir C.; Arab J. Basic Appl. Sci., 2014; 15, 28–34.
[15]. Parekh J., Chanda S.; Afr. J. Biomed. Res., 2006; 9(2), 89–93.
[16]. Khalil M.M., Ismail E.H., Mohamed G.G. et al.; Open J. Chem., 2012; 2(2), 13–21.
[17]. Ejidike I.P., Ajibade P.A.; Rev. Inorg. Chem., 2015; 35(4), 191–222.
[18]. Lipinski C.A.; Drug Discov. Today Technol., 2004; 1(4), 337–341.