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MODIFICATION AND BIOLOGICAL ACTIVITY OF IMINE DERIVATIVE OF AMOXICILLIN

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Abstract:

In this study, we report a novel imine-amoxicillin synthesis (A-C) by reacts amoxicillin with different aldehydes such as 2-hydroxybenzaldehyde, 4-methoxybenzaldehyde, and 4-butoxybenzaldehyde. The derivatives (A-C) were characterized by spectroscopic technique, such as FT-IR and 1H-NMR spectroscopy. All the synthesized derivatives (A-C) were evaluated in vitro against different microorganisms such as Bacillus subtilis, Streptococcus pneumonia, E. coli, and Bacillus subtilis by zone inhibition method. The findings demonstrated that certain derivatives exhibit superior antibacterial properties in comparison to the efficacy of the original drug.

Keywords: Imine, Amoxicillin, Schiff base, Bacteria.

Introduction

Antibiotic medications are used to treat infections and diseases caused by bacteria [1]. They have made a major contribution to improving human health and life expectancy. Many diseases that once killed people can now be treated effectively with antibiotics [2]. However, some strains of bacteria have become resistant to antibiotics. This is called antimicrobial resistance, also known as antibiotic resistance [3].

Certain kinds of bacteria have acquired resistance to previously prevalent drugs in their treatment [4]. Staphylococcus aureus and Neisseria gonorrhoeae have exhibited a high degree of resistance to benzylpenicillin in contemporary times [5]. Historically, penicillin was typically employed to manage these infections [6]. The prevalence of antibiotic resistance is on

the rise globally. Amoxicillin, often known as AMX, is a semisynthetic β-lactam antibiotic with a moderate-spectrum [7, 8]. It is effective against a broad spectrum of Gram-positive bacteria and a limited range of Gram-negative bacteria. The medicine in question was introduced to the market in 1972 and continues to be widely employed within its class due to its superior oral absorption compared to other β-lactam antibiotics [9, 10].

A carbon-nitrogen double bond is a characteristic component of an imine functional group [11, 12]. Carbon atoms are covalently bonded to two aromatic groups or hydrogen atoms. Imines exhibit a lack of nucleophilicity; however, they possess somewhat lower electrophilicity than aldehydes or ketones [13]. The reduced electronegativity of nitrogen compared to oxygen is responsible for the diminished electrophilicity of imine compared to aldehydes or ketones.

In this study, new imine derivatives (A-C) were synthesized and characterized FTIR and ^{1}H-NMR and screened for antimicrobial activities.

Material and Methods

Materials

All chemical used in this study were obtained from sigma Aldrich and Merch companies. [14]

Methods

Synthesis of imine-amoxicillin

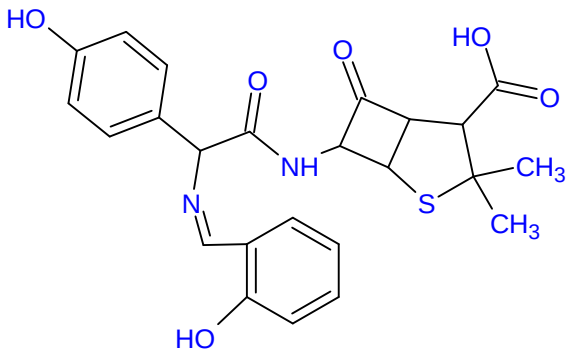
Dissolve (0.419 g, 1.0 mmol) of amoxicillin trihydrate in 20 ml of ethanol. Added (1.0 mole) of corresponding aldehydes, such as 2-hydroxybenzaldehyde, 4-methoxybenzaldehyde, and 4-butoxybenzaldehyde to this solution. The resulting mixture was reflux for 4 h. The precipitates collected, and washed several times with absolute ethanol, dried under vacuum and kept [15, 16].

Investigation of the antimicrobial activity of amoxicillin and Imine- amoxicillin derivatives (A-C).

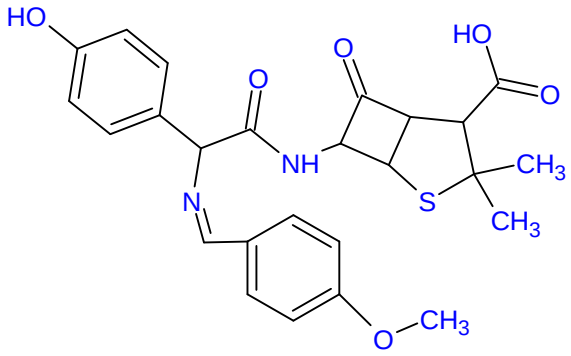
The several bacterial strains, including *Bacillus subtilis*, *Streptococcus pneumonia*, *E. coli*, and *Bacillus subtilis*, were cultivated on Muller-Hinton agar plates using sterile loop and streaking techniques, beginning with the broth culture . Subsequently, a distinct well was generated within the agar medium. A volume of 100 µl of the suitable dilution of amoxicillin and imine-amoxicillin compounds (A - C) was supplied to each well, resulting in efficient absorption. The container was sealed tightly and placed in an incubator set at a temperature of 37 ºC for the duration of the night, with the intention of examining it the following day [14, 17].

Results and Discussion

The spectroscopic result, the appeared azomethine group in FTIR and disappeared amine group of amoxicillin drug and appeared proton of azomethine group of imine-amoxicillin at ^{1}HNMR. Imine derivative (A): Molecular Formula: $C_{24}H_{24}N_2O_6S$, Color: Light yellow powder, M.p.: 231-233 °C, Yield: 73%. FTIR (cm^{-1}): 3416 (OH), 3040 (C-H aromatic), 1667 (C=N), 1594 (C=C aromatic). ^{1}H-NMR (ppm): 9.85 (s, 1H, OH), 8.25 (s, 1H, N=CH), 7.31-7.71 (m, 8H, Ar), 1.44 (d, 3H, CH_3) [17, 18].



Imine derivative (B): Molecular Formula: $C_{49}H_{50}N_4O_{12}S_2$, Color: yellow powder, M.p.: 218-220 °C, Yield: 76%. FTIR (cm^{-1}): 3351 (OH), 3039 (C-H aromatic), 1644 (C=N), 1591 (C=C aromatic). ^{1}H-NMR (ppm): 9.93 (s, 1H, OH), 8.28 (s, 1H, N=CH), 7.04-7.53 (m, 8H, Ar), 1.52 (d, 3H, CH_3) [19].



Imine derivative (C): Molecular Formula: $C_{50}H_{52}N_4O_{12}S_2$, Color: yellow powder, M.p.: 224-226 °C, Yield: 76%. FTIR (cm^{-1}): 3351 (OH), 3039 (C-H aromatic), 1644 (C=N), 1591 (C=C aromatic). ^{1}H-NMR (ppm): 9.81 (s, 1H, OH), 8.61 (s, 1H, N=CH), 7.16-7.79 (m, 8H, Ar), 2.49 (d, 3H, CH-CH_3), 1.52 (t, 3H, CH_3) [20].

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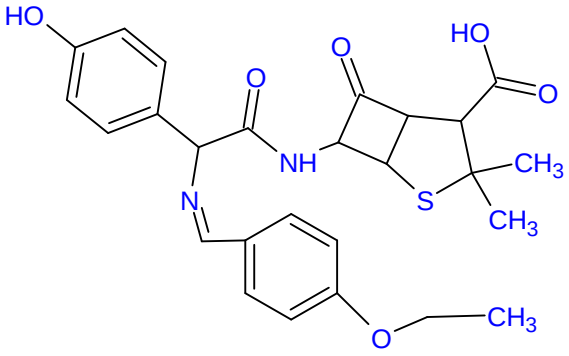


Bioactivity: Table 1 illustrates the results of screening a novel group of imine-amoxicillin compounds (A-C) for their *in vitro* antimicrobial or antibacterial properties. Upon analysis of the inhibitory zone data about *Bacillus subtilis*, *Streptococcus pneumonia*, *E. coli*, and *Bacillus subtilis*, it is evident that the majority of the novel Imine-amoxicillin exhibited superior antibacterial efficacy compared to the original amoxicillin compound. The level of bioactivity exhibits a positive correlation with the concentration. The biggest effect on bacteria was on *E. Coli* by derivative A [21]. The less effect on bacteria was on *Streptococcus pneumonia* by derivative B as shown in table 1.

Table 1: This study investigates the antibacterial properties of amoxicillin and its produced imine compounds (A-C).

Derivative	Zone inhibition (mm)			
	Bacillus subtilis	*E. coli*	*Streptococcus pneumonia*	*Bacillus subtilis*
ceftriaxone	23	18	21	22
A	26	17	24	24
B	21	16	21	21
C	24	16	22	22

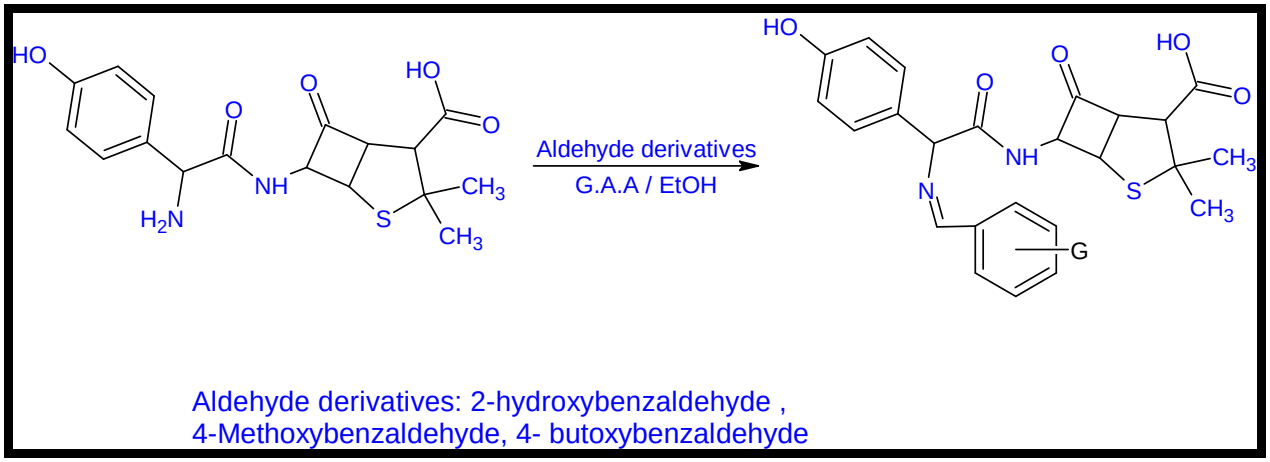
The biggest effect on Fungal was on *Aspergillus nigaer* by derivative A. The derivative A more biological activity from amoxicillin drug which that more activity from derivative C [22], as shown in table 2.

Table 2: The present study investigates the antifungal properties of amoxicillin and its imine compounds (A and C).

Derivative	Zone inhibition (mm)	
	Candida	*Aspergillus nigaer*
Amoxicillin	25	27
A	27	32
C	25	29

The mode of action of β-Lactams entails the interference with the process of peptidoglycan synthesis, a vital component of the cellular membranes of Gram-positive bacteria. The last transpeptidation phase in the creation of the peptidoglycan layer is facilitated by transpeptidases, which are proteins that bind to penicillin [23]. The persistence of the β -lactam nucleus binding to the penicillin-binding proteins leads to the disruption of the cell wall structure, hence impeding the final crosslinking process (transpeptidation) between the linear peptidoglycan polymer chains. Consequently, when combined, it broadens the range of AMX's efficacy to include bacterial strains that exhibit susceptibility to AMX and exhibit β-lactamase production. The development of β-lactamase production has become increasingly significant in respiratory infections, such as H. influenzae and M. catarrhalis [24].

AMX is effectively absorbed in the gastrointestinal (GI) tract after being taken orally as a solution or tablet. However, differences have been observed in the absorption of AMX in various regions of the gastrointestinal tract, with notable absorption taking place in the upper small intestine and minimal absorption in the colon. AMX demonstrates an oral bioavailability that spans from 70% to 90%, with the highest levels of the drug reaching the bloodstream within 60 to 90 minutes after consumption [25].



Scheme 1: Routs of imine-amoxicillin derivatives.

Conclusion

Imine derivative derivatives (A-C) were synthesized and characterized by FTIR and 1H-NMR. Chemical reactions between amoxicillin drug and aldehyde derivatives began the synthesis. The antimicrobial activity of imine derivatives, including amoxicillin, against *Staphylococcus epidermidis, Pseudomonas aeruginosa*, and *Escherichia coli* were tested *in vitro*. The findings demonstrated that certain derivatives exhibit superior antibacterial properties in comparison to the efficacy of the original drug. In future, we will synthesize a new derivative and tested *in vitro*.

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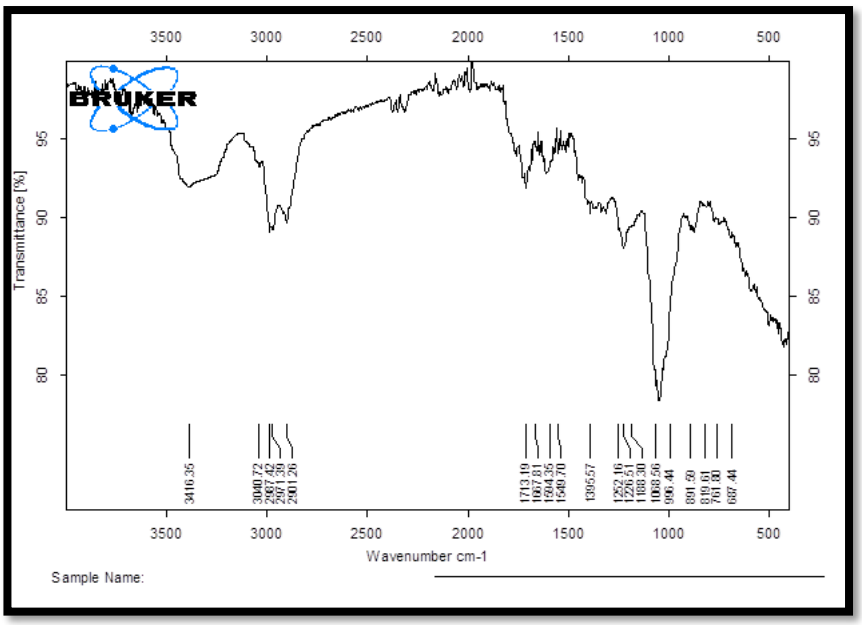

Figure 1: FTIR of derivative A.

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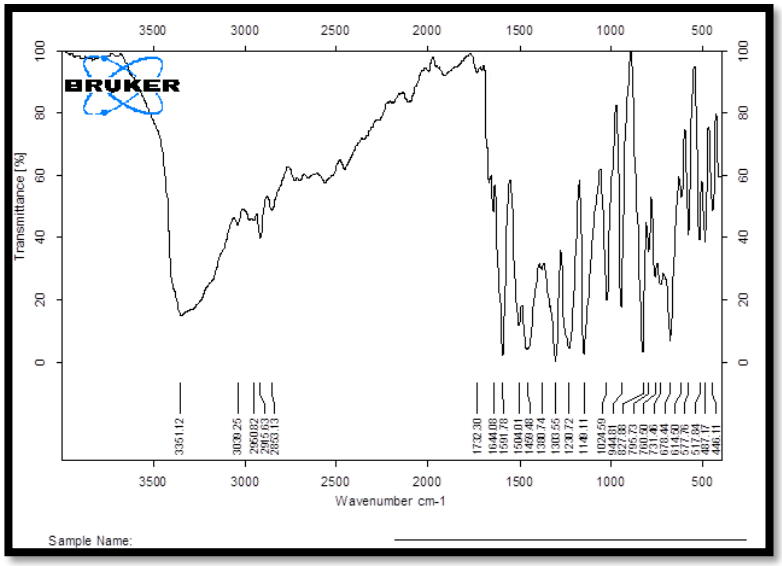

Figure 2: FTIR of derivative B.

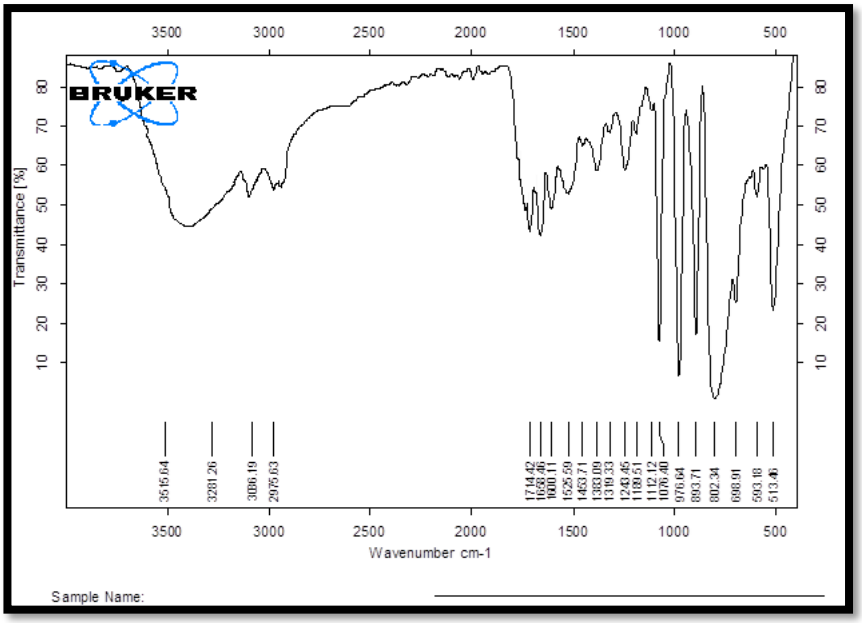

Figure 3: FTIR of derivative C.

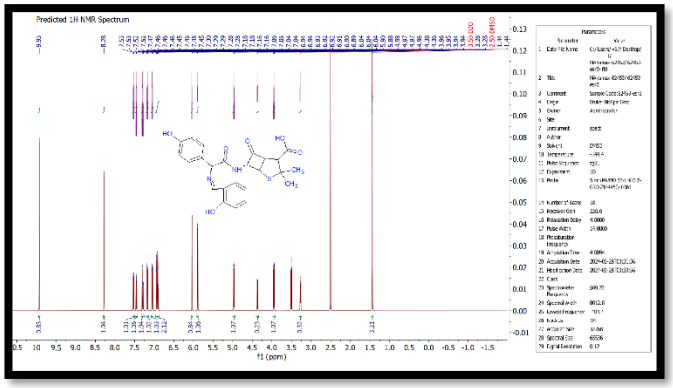

Figure 4: 1H-NMR of derivative A.

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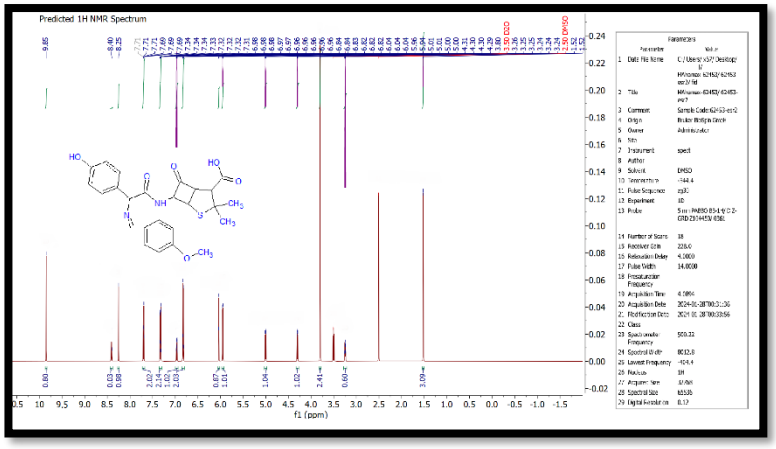

Figure 5: 1H-NMR of derivative B.

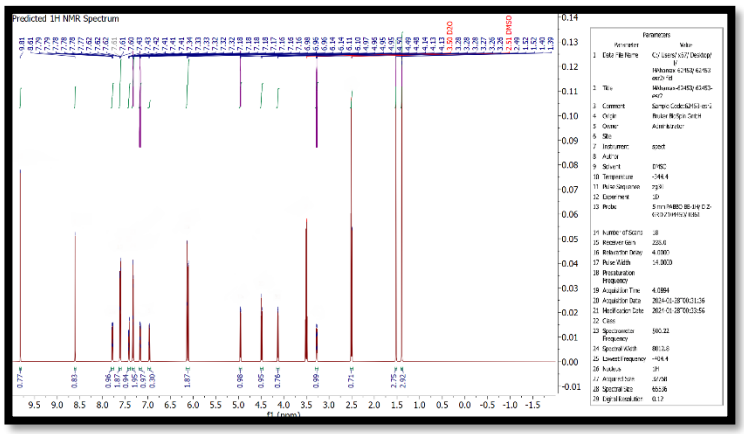

Figure 6: 1H-NMR of derivative C.