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Synthesis, Antibacterial, and Antioxidant Activities of Some Schiff Bases

Hala Sabry Al-Atbi[1], Hassan A. Jaraf[2], Asmaa B. Sabti[3]*

[1]*Department of Chemistry, College of Sciences, University of Basrah, Iraq*
[2]*General Directorate of Education, Basrah, Iraq*
[3]*Department of Chemistry, College of Sciences, University of Misan, Iraq*

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ABSTRACT

Schiff bases are imine (-C=N-) containing compounds having beneficial biological properties, such as anticancer, antibacterial, and antioxidant. Interest in such compounds has grown, inspiring researchers to develop more active and less toxic compounds. Thus, the present study was aimed at synthesizing some Schiff bases and evaluating them for antibacterial and antioxidant activities. Based on ortho vanillin, a variety of Schiff bases (compounds 1–7) were synthesized by the condensation method with substituted amines. The synthesized compounds were characterized using CHN analysis, FT-IR, and ^{1}H-NMR techniques. The *in vitro* antibacterial activity of the compounds was evaluated against gram-negative *Escherichia coli* and gram-positive *Staphylococcus aureus* using the agar well diffusion method. Furthermore, the antioxidant potential of the compounds was determined by the DPPH (2,2-diphenyl-1-picrylhydrazyl) assay. The results showed that all the synthesized compounds had significant antibacterial and antioxidant activities. Compounds 3 and 4 inhibited the test microorganisms most effectively, with an inhibition zone of 35 mm. When compared to the reference compound ascorbic acid (48.7%), compound 5 demonstrated a more powerful suppression of the DPPH radical (28 %) among the imines. The findings of this study suggest that these imines may have therapeutic potential, but more *in vivo* research into their safety and efficacy is needed.

Keywords: Antibacterial, Antioxidant, DPPH, Schiff bases, Synthesis.

Introduction

Schiff bases, also known as azomethines and imines, are a remarkable group of compounds composed of the azomethine group (C=N) with the common formula $R_1HC=N-R$, where R_1 and R are aliphatic, aromatic, or heterocyclic groups.[1,2] Hugo Schiff invented these compounds in 1864 by the condensation reaction of carbonyl compounds with primary amines.[3] Many scientists have synthesized and published numerous imine compounds due to their synthetic flexibility and relative ease.[4] Schiff bases are used in many fields, including supramolecular chemistry, material sciences, inorganic and organic chemistry, and biological chemistry.[5,6] Because of their broad spectrum of biological actions, Schiff bases have gained importance in the medical field. These compounds have anti-HIV, antimalarial, antibacterial, anti-tuberculosis, antioxidants, analgesic, antiamoebic, antispasmodic, antifungal, anti-cancer, anthelmintic, and anti-inflammatory properties.[7,8] Many organic compounds are synthesized primarily for their potential chemotherapeutic effects. It has now been demonstrated that the toxicity of Schiff bases is specific to a particular microorganism. Bacteria are widely distributed and can be found almost anywhere. Chemicals such as antiseptics, disinfectants, and antibiotics are employed in our daily lives to eliminate or inhibit the growth of microorganisms. Antibiotic resistance, which is a microorganism's ability to tolerate the effects of antibiotics, necessitates the synthesis of active compounds. The evolution of resistance to chemotherapeutics in many germ types has posed a substantial challenge in germ therapy, necessitating the development of novel chemotherapeutic medications.[9,10]

*Corresponding author. E mail: asmaabadr@uomisan.edu.iq
Tel: 009647717808726

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The ability of antioxidants to protect cells and organisms from oxidative stress-induced damage has been investigated in several studies. Fresh natural or synthetic chemicals that potentially offer active constituents to eliminate or minimize the effects of oxidative stress on cells have aroused the interest of scientists from several fields.[11] This study was conducted to synthesize and characterize a variety of Schiff bases derived from the reaction of ortho vanillin with different amines. The synthesized imines were also tested for *in vitro* antibacterial and antioxidant activities.

Materials and Methods

Reagents used

The reagents used for the study include benzene-1,4-diamine, naphthalene-1-amine, 2-(4-aminophenyl) acetic acid, 2-methyl-4-nitro aniline, pyridine-2-amine, 4-nitroaniline, 4-chloroaniline, 2-hydroxy-3-methoxy benzaldehyde (ortho-vanillin), DPPH, and ascorbic acid. All solvents were of analytical grade, obtained from Merck and Fluka, and used exactly as received.

Instrumental analysis

The Gallenkemp (England) melting point apparatus was used to determine melting points. Infrared (IR) spectra were verified by the Shimadus FTIR-8400 device (Japan). Proton nuclear magnetic resonance (^{1}H-NMR) ranges were measured in deuterated dimethyl sulfoxide (DMSO-d6) solvent with a JEOL-JNM-EX 400 MHz device (Japan). The chemical shifts are presented in parts per million (ppm) units, using tetramethylsilane (TMS) as a reference. The elemental analyzer Eurovector EA-3000 A was used to perform the elemental analysis (C, H, and N).

Synthesis of Schiff bases

The aromatic aldehyde ortho vanillin (1 mmol) in 20 mL of ethanol was thoroughly mixed with two drops of glacial acetic acid and heated for 5 minutes. Then (1 mmol) of amine [benzene-1,4-diamine, naphthalene-1-amine, 2-(4-aminophenyl) acetic acid (1 mmol), 2-

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methyl-4-nitroaniline, pyridine-2-amine, 4-nitroaniline, 4-chloroaniline, and 2-hydroxy-3-methoxy] in ethanol were progressively added to the initial solution. The mixture was refluxed for 5-6 hours. The reaction process was monitored using a TLC plate and an acetone: chloroform (7:3) eluent. The product was cooled to room temperature before drying, and recrystallized by ethanol.[12]

Evaluation of antibacterial activity

The Schiff base compounds were evaluated for *in vitro* antibacterial activity against gram-negative *Escherichia coli* (ATTC25922) and gram-positive *Staphylococcus aureus* (ATCC 25923) using the agar well diffusion assay.[13] Muller Hinton agar (MH) was used as the culture medium, and a concentration of 30 mg/mL of test samples in DMSO was employed. DMSO was used as a negative control, while amoxicillin was used as a positive control. The microbe inoculums were evenly spread on a sterile Petri plate MH agar using a clean cotton swab. Each well received 50 uL from each concentration of chemical products. Every well was 20 mm apart, and the agar gel was around 7 mm in diameter. The cultures were incubated at 36^{o}C for 24 hours under aerobic conditions. After incubation, the inhibition of microbial growth was detected, and measured in mm using the Vernier caliper.

Determination of antioxidant activity using the DPPH assay

The activity of prepared Schiff bases as antioxidants was determined using the 2,2-diphenyl-1-picrylhydrazyl (DPPH) assay.[14] The DPPH methanol solution (20 µg/mL) was stored in the dark at 10^{o}C until use. All compounds were synthesized at a concentration of 1 mg/mL in DMSO. Following the addition of 0.5 mL of each sample to the DPPH solution (1.0 mL), the absorbance was measured at 517 nm after 30 minutes of incubation in the dark. The DPPH radical absorbance without antioxidants was measured as a control. Vitamin C was used as a positive control for the measurement. All tests were performed in three replicates. The inhibition of DPPH radical by samples was calculated using equation 1:

% DPPH inhibition = (Ac – As) x100/Ac …… (1)

Where Ac is the absorbance of the control and As is the absorbance of the sample.

Results and Discussion

The most common method for producing Schiff bases is to mix an aromatic aldehyde with a suitable amine. Schiff bases (imines) were produced under reflux conditions, and glacial acetic acid was utilized as a catalyst to increase the electrophilicity of the carbonyl group. The synthesized Schiff bases (Figure 1) were characterized by different techniques, as in following data:

2-[(4-aminophenylimino) methyl]-6-methoxyphenyl (1): orange powder, reaction time: 5hr, Rf = 0.68, yield: 55%, mp 238-240 °C, IR (KBr, cm^{-1}): 3448(OH), 3421-3383(NH_2), 2982(CH-aliph.), 1608(HC=N), and 1253(C-O). ^{1}H-NMR (400 MHz, DMSO-d_6); δ /ppm: 13.19 (s, 1H), 9.02 (s, 1H), 7.54 (s, 3H), 7.26 (d, *J* = 7.5 Hz, 1H), 7.14 (d, *J* = 8.0 Hz, 1H), 6.93 (t, *J* = 7.9 Hz, 1H), 3.83 (s, 3H). Calculated elemental analysis for $C_{14}H_{14}N_2O_2$: C, 69.41; H, 5.82; N, 11.56. found: C, 69.11; H, 5.70; N, 11.34.

2-methoxy-6-[(naphthalene-1-ylimino) methyl] phenol (2): maroon powder, reaction time: 5hr, Rf = 0.8, yield: 42%, mp 75-77°C. IR (KBr, cm^{-1}): 3448(OH), 3055(CH-aromatic), 2939(CH-aliph.), 1612(HC=N), and 1249(C-O). ^{1}H-NMR (400 MHz, DMSO-d_6); δ /ppm: 13.25 (s, 1H, OH), 9.01 (s, 1H), 8.17 (d, *J* = 8.2 Hz, 1H), 7.98 (d, *J* = 7.0 Hz, 1H), 7.87 (d, *J* = 8.0 Hz, 1H), 7.63 – 7.58 (m, 3H), 7.56 (d, *J* = 8.3 Hz, 1H), 7.43 (d, *J* = 7.1 Hz, 1H), 7.33 (d, *J* = 7.7 Hz, 1H), 7.17 (d, *J* = 7.8 Hz, 1H), 6.95 (t, *J* = 7.7 Hz, 1H), 3.86 (s, 3H). Calculated elemental analysis for $C_{18}H_{15}NO_2$: C, 77.96; H, 5.45; N, 5.05. found C, 77.81; H, 5.22; N, 4.81.

2-[4-(2-hydroxy-3-methoxybenzylideneamino) phenyl] acetic acid (3): orange crystal, reaction time: 5hr, Rf = 0.25, yield: 61%, mp. 170-172 °C. 1R (KBr, cm^{-1}): 3452(OH), 3024(CH-aromatic), 2914(CH-aliph.), 1697(COOH), 1616(HC=N), and 1253(C-O). ^{1}H-NMR (400 MHz, DMSO-d6); δ /ppm: 13.28 (s, 1H, OH), 8.96 (s, 1H, N=CH), 7.39 – 7.33 (m, 4H), 7.23 (d, *J* = 7.8 Hz, 1H), 7.13 (d, *J* = 7.9 Hz, 1H), 6.91 (t, *J* = 7.9 Hz, 1H), 3.82 (s, 3H), 3.61 (t, 2H). Calculated elemental analysis for $C_{16}H_{15}NO_4$: C, 67.36; H, 5.30; N, 4.91. found: C, 67.11; H, 5.12; N, 4.75.

2-methoxy-6-[(2-methyl-4-nitrophenylimino methyl] phenol (4): orange powder, reaction time: 5hr, Rf = 0.91, yield: 47%, mp 150-152 °C. IR (KBr, cm^{-1}): 3448(OH), 3001(CH-aromatic), 2939(CH-aliph.), 1612(HC=N), 1516-1465(NO_2), and 1257(C-O). ^{1}H-NMR (400 MHz, DMSO-d_6); δ /ppm: 12.53 (s, 1H), 8.92 (s, 1H), 8.21 (s, 1H), 8.16 (d, *J* = 9.4 Hz, 1H), 7.49 (d, *J* = 8.5 Hz, 1H), 7.32 (d, *J* = 7.8 Hz, 1H), 7.19 (d, *J* = 8.0 Hz, 1H), 6.95 (t, *J* = 7.7 Hz, 1H), 3.84 (s, 3H), 2.41 (s, 2H). Calculated elemental analysis for $C_{15}H_{14}N_2O_4$: C, 62.93; H, 4.93; N, 9.79. found: C, 62.56; H, 4.72; N, 9.64.

2-methoxy-6-[(pyridine-2-ylimino) methyl] phenol (5): orange powder, reaction time: 5hr, Rf = 0.5, yield: 18%, mp 85-87 °C. IR (KBr, cm^{-1}): 3448(OH), 3055(CH-aromatic), 2955(CH-aliph.), 1608(HC=N), 1585(C=N ring), and 1253(C-O). ^{1}H-NMR (400 MHz, DMSO-d_6); δ/ppm: 13.14 (s, 1H), 9.48 (s, 1H), 8.53 (d, *J* = 3.4 Hz, 1H), 7.95 – 7.90 (m, 1H), 7.45 (d, *J* = 7.8 Hz, 1H), 7.35 (d, *J* = 7.0 Hz, 3H), 7.17 (d, *J* = 5.8 Hz, 1H), 6.92 (t, *J* = 7.8 Hz, 1H), 3.83 (s, 3H). Calculated elemental analysis for $C_{13}H_{12}N_2O_2$: C, 68.41; H, 5.30; N, 12.27. found: C, 68.23; H, 5.15; N, 12.19.

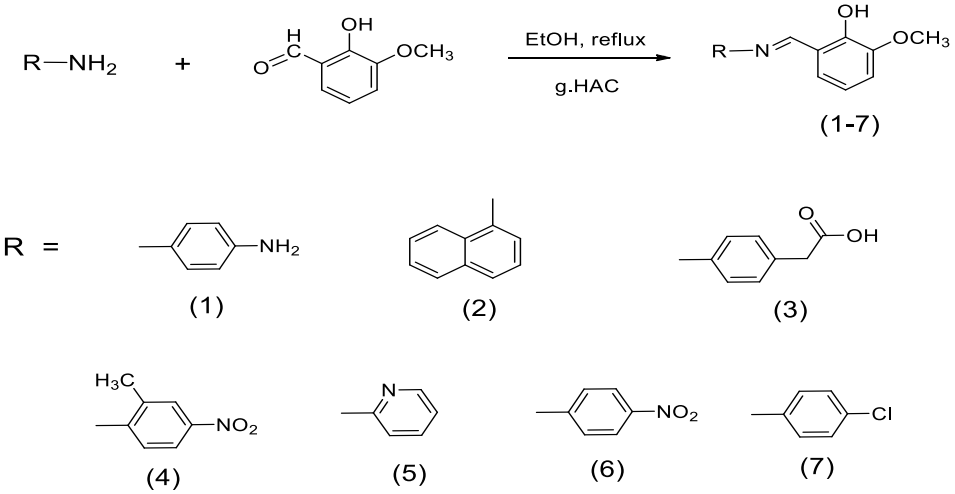

Figure 1: Synthesis of Schiff bases.

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2-methoxy-6-[(4-nitrophenylimino) methyl] phenol (6): red crystal, reaction time: 6hr, Rf = 0.88, yield: 85%, mp 165-166 °C. IR (KBr, cm^{-1}): 3448(OH), 3063(CH-aromatic), 2935(CH-aliph.), 1608(HC=N), 1516-1462 (NO_2), and 1261(C-O). ^{1}H-NMR (400 MHz, DMSO-d_6); δ /ppm: 12.32 (s, 1H), 8.95 (s, 1H), 8. 32 (s, 1H), 8.16 (d, *J* = 9.4 Hz, 1H), 7.49 (d, *J* = 8.5 Hz, 1H), 7.32 (d, *J* = 7.8 Hz, 1H), 7.19 (d, *J* = 8.0 Hz, 1H), 6.94 (t, *J* = 7.6 Hz, 1H), 3.82 (s, 3H). Calculated elemental analysis for $C_{14}H_{12}N_2O_4$: C, 61.76; H, 4.44; N, 10.29. found: C, 61.54; H, 4.21; N, 10.10.

2-[(4-chlorophenylimino) methyl]-6-methoxyphenol (7): orange crystal, reaction time: 5hr, Rf = 0.9, yield: 80%, mp 95-96 °C. IR (KBr, cm^{-1}): 3479(OH), 3055(CH-aromatic), 2943(CH-aliph), 1612(HC=N), ,1257(C-O) and 732(C-Cl). ^{1}H-NMR (400 MHz, DMSO-d_6); δ /ppm: 12.92 (s, 1H), 8.95 (s, 1H), 7.51 (d, *J* = 8.7 Hz, 3H), 7.44 (d, *J* = 7.8 Hz, 3H), 7.24 (d, *J* = 7.7 Hz, 1H), 7.14 (d, *J* = 7.9 Hz, 1H), 6.91 (t, *J* = 7.9 Hz, 1H), 3.82 (s, 3H). Calculated elemental analysis for $C_{14}H_{12}ClNO_2$: C, 64.25; H, 4.62; N, 5.35. Found C, 63.90; H, 4.31; N, 5.21.

The FT-IR technique was used to characterize all the Schiff bases. The stretching vibration of the hydroxyl group was found in the FT-IR spectra of all Schiff bases, with absorption bands 3421-3479 cm^{-1}. In addition, there are absorption bands for aromatic C-H at 3001-3063 cm^{-1} and the azomethine group (N=CH) at 1608-1616 cm^{-1}. The non-appearance of the band in the range of 1700-1750 cm^{-1} also demonstrates that the (-CHO) group has been converted to the (N=CH) group. In DMSO-d_6/solvent, the compounds' (^{1}H-NMR) spectra were obtained, and structural assignments are listed above. The (-OH) group singlet signals were detected in the range of 12.3-13.2 ppm scopes of all substances. ^{1}H-NMR spectra of all imines revealed a sharp singlet at 8.9-9.4 ppm, denoting the entity of the azomethine (N=CH) proton, and a singlet signal at 3.6 and 2.4 ppm, indicating the presence of the CH_2 proton in compounds 3 and 4, respectively. The (-OCH_3) group appeared as a sharp singlet at 3.8 ppm. Due to hydrogen bonding, the proton of the carboxylic group (COOH) in compound 3 emerged as a broad singlet. At 6.8-8.5 ppm, multiple signals belong to aromatic protons.[15,16] Furthermore, the CHN results are consistent with the hypothesized structures.

Antibacterial activity of synthesized Schiff bases

The antibacterial activity of the Schiff bases was evaluated *in vitro* against human pathogens (*Staphylococcus* aureus and *Escherichia coli*) using the agar well diffusion method.

The results are shown in Table 1 and Figure 2. At a concentration of 30 mg/mL, all of the compounds demonstrated promising antibacterial activity against the two bacterial strains. Compared to the conventional antibiotic amoxicillin, which had an inhibition zone of 12-15 mm, compounds 3 and 4 were more effective against the two bacterial species with an inhibition zone of 35 mm. The activity of the other Schiff bases was also good, with inhibition zones ranging from 13-30 mm.

The antimicrobial activity of any molecule is confounded by a complex combination of electronic, pharmacokinetic, and steric factors. Also, the mechanism of action of various antimicrobials involves several targets in bacteria. According to a previous study published in 2008 by Joseyphus and Nair,[17] the mechanism for antimicrobials involves the interference with the synthesis of the cell wall, resulting in altered cell permeability, or disorganizing lipoproteins, resulting in cell death. This process is responsible for the variation in the efficiency of various chemicals against various microbes and is dependent on cell impenetrability or differences in organism ribosomes.

Table 1: Antibacterial screening (zone of inhibition in mm) of synthesized Schiff bases

Compound	Inhibition zones (mm)	
	E. coli	***S. aureus***
1	13	16
2	18	20
3	35	35
4	35	35
5	30	27
6	30	30
7	17	15
Amox	15	12
C	NI	NI

1-7: Synthesized compounds 1-7, respectively; *S. aureus*: *Staphylococcus aureus*; *E. coli*: *Escherichia coli*; Amox: Amoxicillin; C: DMSO (dimethyl sulfoxide); NI: No Inhibition.

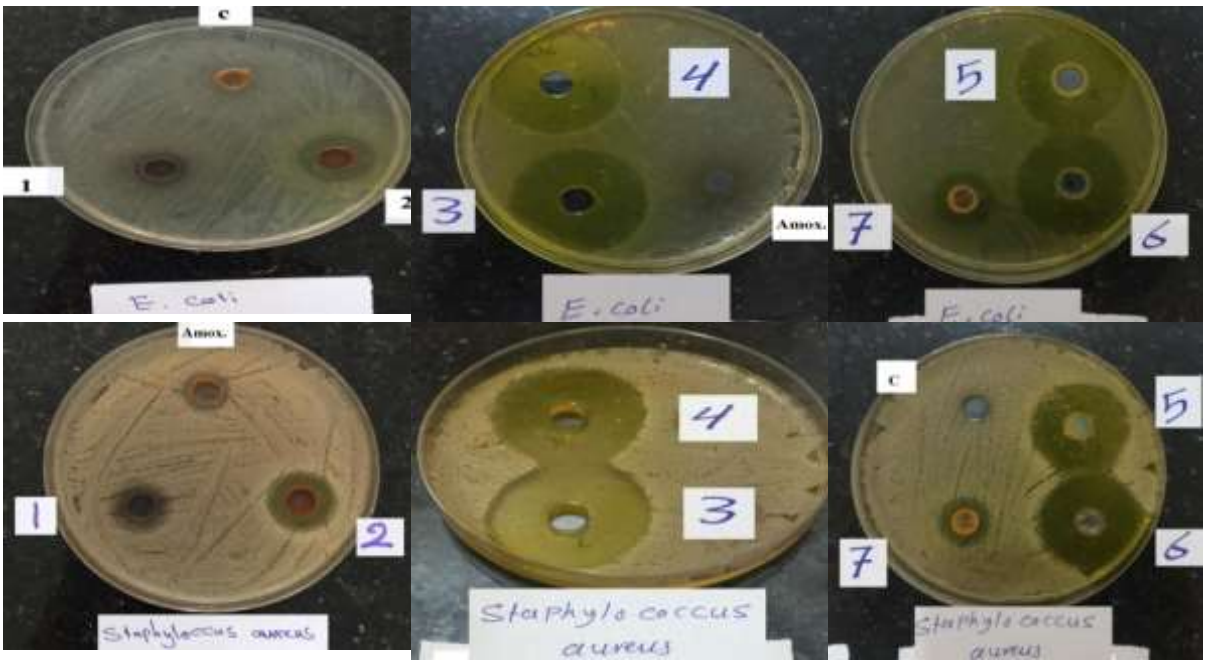

Figure 2: Antibacterial activity of synthesized Schiff bases against *Escherichia coli* and *Staphylococcus aureus* as indicated by inhibition zones.

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Inhibiting a stage in the synthesis of the peptidoglycan layer, which is essential for retaining the organism's form, could potentially result in the termination of the bacteria's cell wall structure, which is required for bacteria survival.[18] Another reported mechanism of antibacterial mechanism of action includes the deactivation of several cellular enzymes involved in the bacterial metabolic processes and interference with normal cell activities by forming a hydrogen bond between active groups (ex. azomethine group) and the active centers of cell components. Phenolic compounds are also known for their antibacterial characteristics because they can interact with membrane proteins via hydrogen bonds formed by hydroxyl groups. This interaction can cause changes in membrane permeability, which can lead to cell death, as well as disruption of typical cellular pathways due to the denaturation of particular cell proteins.[19] Schiff bases have been identified as antibacterial promoters and are widely used as therapeutic and antibacterial agents. The azomethine group is found in drugs such as nifuroxazide (INN) and thiacetazone.[20,21] Previous research has found that Schiff bases containing the ortho-vanillin moiety are good antibacterial agents.[22] The activity of synthesized Schiff bases can be attributed to various active groups such as imine and hydroxyl, which can form hydrogen bonds with numerous cellular components. Furthermore, halogen atoms and the phenyl rings give the compound a lipophilic nature, allowing it to easily penetrate microbial cell walls.[23]

Antioxidant activity of synthesized Schiff bases

Antioxidants are naturally occurring compounds that protect living organisms from free radicals, which are harmful molecules. Free radicals are involved in the etiology of various illnesses, including liver injury, diabetes, cancer, heart diseases, autoimmune disorders, aging, and atherosclerosis. Consequently, antioxidants are important in the treatment and prevention of various diseases. Synthetic antioxidants are now widely used in place of natural antioxidants because they are more practical and less expensive.[24,25] The stable free radical DPPH has an unusual electron in its structure, which is often used to assess the antioxidant activity of inorganic and organic substances. The DPPH radical scavenging activity of compounds can be observed visually as a change in the color of the solution. When DPPH-H is reduced to its non-radical state by a proton or electron donor, the DPPH• color changes from violet to yellow (equation 2).[26,27] The DPPH exhibits the maximum absorption in the 515-520 nm absorption region. As a result, the decrease in DPPH absorbance can be used to measure the free radical inhibition activity.[28]

DPPH• +AH → DPPH (H) + A …… (2)

In Table 2, the scavenging ability of compounds was expressed as a percentage of inhibition. When compared to the other imines, compound 5 demonstrated the highest DPPH radical scavenging activity. It was, however, lower than vitamin C. Compounds 1 and 3 also demonstrated moderate DPPH scavenging activity.

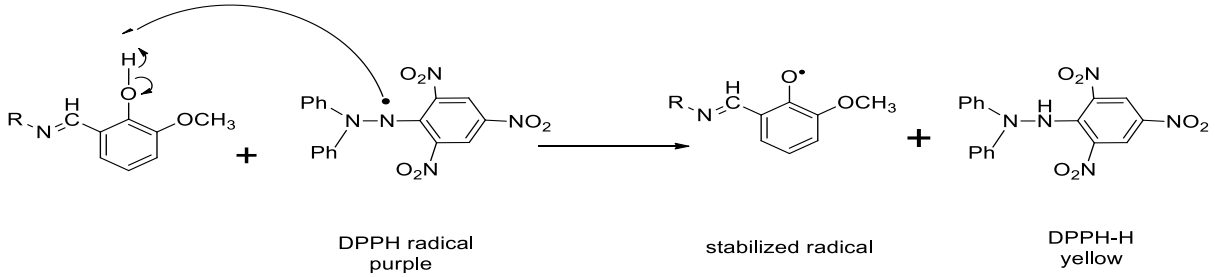

Figure 3: Proposed mechanism of action of the synthesized imines as antioxidants.

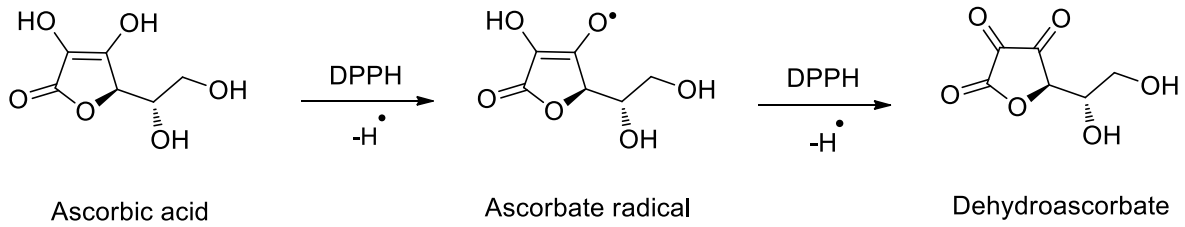

Figure 4: Proposed mechanism of action of ascorbic acid as antioxidant.

Table 2: The DPPH inhibition percent (%) for Schiff bases and ascorbic acid

Compound (1 mg/mL)	% DPPH inhibition
1	17.75
2	11.52
3	18.02
4	10.57
5	28.01
6	0
7	8.95
8	48.78

1-7: Synthesized compounds 1-7, respectively; 8: Vitamin C

Compounds 2, 4, and 7 showed negligible DPPH radical scavenging activity when compared to vitamin C. On the other hand, compound 6 was observed to be inactive. All the synthesized Schiff bases contain the phenol group. It is widely known that phenolic compounds, even at low concentrations, can inhibit the oxidation process. These compounds transfer protons from the hydroxyl moiety to free radicals and transform into the resonance stabilized phenoxide radical ($ArO^{\cdot}$).[29-31] All of the compounds demonstrated lower antioxidant activity than ascorbic acid, probably because imines only have a proton to donate in terms of radical stabilization (Figure 3). In contrast, ascorbic acid can donate both protons to the DPPH radical to create dehydroascorbate, as depicted in Figure 4.

Conclusion

A variety of Schiff bases were synthesized, and their structures were determined using CHN analysis, infrared, and ^{1}H-NMR spectroscopy. Synthesized imines were tested for antibacterial and antioxidant properties. All compounds had strong antibacterial activity, compound 3 (containing an acetic acid moiety) and compound 4 (2-methyl-4-nitrobenzene moiety) being the most effective. The synthesized imines showed significant antioxidant activity, indicating their ability to donate hydrogen atoms to the generated free radicals. These imines

may have therapeutic use, but further *in vivo* studies into their safety and efficacy are required.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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