Synthesis of Some novel Azomethine Oxide Derived from Aromatic Oximes and their Anti-microbial Studies

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***Abstract*—The organic compound category known as azomethine oxides has garnered significant attention due to its potential for bioactive and pharmacological effects, as well as its role in organic syntheses. Existing literature offers various methods for producing derivatives of these compounds. This study, in particular, concentrates on the creation of several aromatic oximes through the reduction of corresponding aldehydes. Furthermore, these oximes are employed in the generation of new azomethine oxides through a condensation reaction with selected aldehydes. The molecular structure of the synthesized azomethine oxides is determined using techniques such as Fourier-transform infrared spectroscopy, ^{1}H-NMR, and ^{13}C-NMR. Finally, the antimicrobial effectiveness of these compounds was assessed against *Escherichia coli* (gram-negative bacteria), *Staphylococcus aureus* (gram-positive bacteria), and *Candida albicans* (fungus). The synthesized compounds were obtained with high purity and yielded excellent results. Furthermore, the data demonstrates that these azomethine oxides exhibit significant antimicrobial activity when compared to standard drugs.**

***Index Terms*—Aromatic oximes, Azomethine-*N*-oxide, Biological activity, Condensation reaction.**

I. Introduction

Nitrone, specifically the azomethine-*N*-oxide, is represented by the chemical structure R'-CH=N(O)-R" in its simplest form. It is a class of organic compounds that contain a nitrogen-oxygen double bond (El Bouakher, Martel, and Comesse, 2019). Nitrones are versatile compounds with diverse applications in organic synthesis and medicinal chemistry (Murahashi and Imada, 2019; Hiraoka, et al., 2019). Nitrones are typically synthesized by the condensation reaction between a carbonyl compound (such as an aldehyde or a ketone) and hydroxylamine, followed by oxidation. This reaction forms the N-O double bond and creates a stable nitronate intermediate, which can be isolated or used directly in subsequent reactions (Murahashi and Imada, 2019). One of the most notable characteristics of nitrones is their ability to undergo 1,3-dipolar cycloaddition reactions with alkenes or alkynes, known as the "nitrone-alkene/alkyne" cycloaddition (Yang, et al., 2017; Alshreimi, et al., 2020). This reaction forms isoxazolidine or isoxazole derivatives, depending on the specific conditions used (Qaddo and Abed, 2022; Li, et al., 2021). The resulting products can have interesting biological activities and can serve as building blocks for the synthesis of more complex molecules (Anderson, et al., 2016). Nitrones are widely used in the synthesis of natural products, pharmaceuticals, and other biologically active compounds (Mohammed and Salih, 2022). They have been employed in the development of drugs for various therapeutic areas, including neurodegenerative diseases, cancer, antimicrobial, antitumor, anti-inflammatory properties, and infectious diseases (Yang, et al., 2017; McKay, et al., 2011; Sandmeier and Carreira, 2021). In addition to their synthetic applications, nitrones also exhibit antioxidant properties, which make them useful in the fields of free radical biology and medicine (Floyd, et al., 2002; Floyd, et al., 2008).

Considering all the aforementioned information, we hereby present the synthesis of several new azomethine-*N*-oxide derivatives and an assessment of their biological properties.

II. Experimental

A. Materials and Instrumentation

The study utilized commercially obtained materials and instrumentation. These included sodium sulfate anhydrous,

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diethyl ether, petroleum ether (Scharlau), NaOH, KOH (SDFCL), HNO_3, methanol (Romil), and methyl orange (BDH). Hydroxylamine hydrochloride and aldehydes were also acquired from a commercial laboratory. The materials and solvents were used directly from their containers without any further purification steps. The uncorrected melting points of the nitrones were determined using a Stuart Scientific melting point apparatus (SMP3). Fourier-transform infrared spectroscopy (FT-IR) spectra were recorded at Salahaddin University-Erbil using a Shimadzu 8300 instrument with KBr disks. ^{1}H-NMR and ^{13}C-NMR spectra were obtained at the Kurdistan Central Research Center in Iran using a 500 MHz and 125 MHz spectrometer, respectively. Tetramethylsilane was used as an internal reference, and deuterated chloroform $CDCl_3$ was used as the solvent. The chemical shifts were measured in units of parts per million (ppm), with the residual solvent as the reference. Coupling constants (J) were reported in Hertz. The ChemDraw software was utilized for the nomenclature of the compounds.

B. Synthesis of Phenylhydroxylamine Derivatives (Kliegel, Metge, and Rettig, 1997)

General Procedure A: 34 mmol, 1.36 g of NaOH was dissolved in 25 mL of H_2O and then 15 mmol of one of the substituted benzaldehydes. The solution was supplemented with 18 mmol, 1.25 g of hydroxylamine hydrochloride, and the resulting mixture was stirred at ambient temperature for duration of 45 min. Subsequently, the solution was acidified by adding 10% aqueous HCl. The resulting mixture was extracted with 3*15 mL of methylene chloride. The organic layer was then dried using anhydrous sodium sulfate (Na_2SO_4) and concentrated by a rotary evaporator.

In the next step, 10 mmol of the obtained material was dissolved in 20 mL of MeOH, and then, 6.7 mmol, 0.42 g of $NaBH_3CN$ was added to it. A very small amount of methyl orange was added to the solution as an indicator. The solution was acidified by adding 4N HCl/MeOH until a pink solution was observed. The mixture was stirred for 1.5 h, which MeOH was removed using a rotary evaporator. To the resulting aqueous solution, 20 mL of H_2O and 4M KOH were added to adjust the pH to 9. The mixture was extracted with 3*15 mL of CH_2Cl_2. The CH_2Cl_2 layer was dried with Na_2SO_4 and removed *via* rotary evaporation.

C. Synthesis of Azomethine Oxides

General Procedure B: In a solution containing *N*-phenylhydroxylamine derivative (10 mmol, 1.0 eq.) in dichloromethane (10 ml), an equivalent amount of aldehyde (10 mmol, 1.0 eq.) was added while stirring. The mixture was then heated to 60°C and stirred until the starting material was fully consumed, as monitored by TLC. The solvent was evaporated under reduced pressure to obtain the crude product, which subsequently precipitated. The resulting precipitate was purified by recrystallization with hot ethanol to obtain pure azomethine oxide. The purified compound was stored in a cool and dark place (Qaddo and Abed, 2022).

(E)-N-benzyl-1-(p-tolyl)methanimine oxide (5)

Following the general procedure B, white crystal (1.8 g, 80%), m.p.= 109–111°C; R_f = 0.51 (10:90 methanol/dichloromethane); ^{1}H-NMR (500 MHz, $CDCl_3$) δ ppm: δ 8.13 (d, 2H, N=C*H* + 1H, aromatic proton), 7.65–7.13 (m, 8H, aromatic protons), 5.05 (s, 2H, Ph-CH_2), (s, 3H, CH_3). ^{13}C-NMR (126 MHz, $CDCl_3$) δ 140.97, 134.43, 133.37, 129.22, 129.21, 129.17, 129.16, 128.95, 128.91, 128.70, 128.69, 128.66, 127.77, 71.01, 21.68.

(E)-N-benzyl-1-(3,4-dimethoxyphenyl)methanimine oxide (6)

Following the general procedure B, light yellow solid (2.4 g, 89%), m.p.= 103–105°C; R_f = 0.36 (10:90 methanol/dichloromethane); ^{1}H-NMR (500 MHz, $CDCl_3$) δ ppm: δ 8.35 (s, 1H, N=C*H*), 7.51–7.29 (m, 8H, aromatic protons), 4.99 (s, 2H, Ph-CH_2), 3.88 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3). ^{13}C-NMR (126 MHz, $CDCl_3$) δ 150.72, 148.42, 134.32, 133.35, 129.21, 129.20, 128.92, 128.91, 128.89, 123.73, 123.17, 110.93, 110.55, 70.78, 70.77, 55.87.

(E)-N-(4-methylbenzyl)-1-phenylmethanimine oxide (7)

Following the general procedure B, white crystal (2.0 g, 88%), m.p.= 116–118°C; R_f = 0.56 (10:90 methanol/dichloromethane); ^{1}H-NMR (500 MHz, $CDCl_3$) δ ppm: δ 8.30–8.20 (m, 1H, aromatic proton), 8.15 (s, 1H, N=C*H*), 7.51–7.17 (m, 8H, aromatic protons), 5.10 (s, 1H, Ph-CH*H*), 2.37 (s, 4H, Ph-C*H*H + CH_3). ^{13}C-NMR (126 MHz, $CDCl_3$) δ 149.95, 149.94, 140.03, 140.00, 135.29, 130.78, 129.74, 129.55, 129.47, 129.13, 128.48, 126.96, 70.74, 21.47, 21.46.

(E)-N-(4-methylbenzyl)-1-(p-tolyl)methanimine oxide (8)

Following the general procedure B, white crystal (2.2 g, 92%), m.p. = 89–91°C; R_f = 0.52 (10:90 methanol/dichloromethane); ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 8.12 (d, J = 7.9 Hz, 2H, aromatic protons + N=C*H*), 7.38–7.12 (m, 7H, aromatic protons), 4.94 (s, 2H, Ph-CH_2), 2.33 (s, 6H, 2*CH_3). ^{13}C-NMR (126 MHz, $CDCl_3$) δ 140.76, 138.71, 134.15, 130.49, 129.57, 129.25, 129.12, 128.69, 127.94, 70.65, 21.67, 21.25.

(E)-1-(3,4-dimethoxyphenyl)-N-(4-methylbenzyl) methanimine oxide (9)

Following the general procedure B, yellow crystal (2.6 g, 91%), m.p.= 66–68°C; R_f = 0.76 (10:90 methanol/dichloromethane); ^{1}H-NMR (500 MHz, $CDCl_3$) δ ppm: δ 8.37 (s, 1H, N=C*H*), 7.45–6.81 (m, 7H, aromatic protons), 4.98 (s, 2H, Ph-CH_2), 3.90 (s, 6H, 2*OCH_3), 2.36 (s, 3H, CH_3). ^{13}C-NMR (126 MHz, $CDCl_3$) δ 148.43, 148.40, 138.93, 138.91, 130.21, 129.67, 129.66, 129.36, 129.31, 123.71, 123.29, 111.06, 110.49, 70.51, 56.05, 55.89, 21.20.

(E)-N-(3,4-dimethoxybenzyl)-1-(p-tolyl)methanimine oxide (10)

Following the general procedure B, white crystal (2.6 g, 91%), m.p.= 100–101°C; R_f = 0.55 (10:90 methanol/dichloromethane); ^{1}H-NMR (500 MHz, $CDCl_3$) δ ppm: 8.05 (d, J = 8.0 Hz, 2H, aromatic protons), 7.30 (s, 1H, N=C*H*), 7.15–6.75 (m, 5H, aromatic protons), 4.88 (s, 2H, Ph-CH_2), 3.79 (s, 6H, 2*OCH_3), 2.27 (s, 3H, Ph-CH_3). ^{13}C-NMR (126 MHz, $CDCl_3$) δ 149.49, 149.09, 140.79, 134.02, 133.96, 129.12, 129.05, 128.63, 128.59, 127.79, 125.76, 122.15, 122.10, 112.40, 112.32, 111.14, 21.62.

(E)-N-(3,4-dimethoxybenzyl)-1-(3,4-dimethoxyphenyl) methanimine oxide (11)

In accordance with the general procedure B, light yellow solid (3.0 g, 91%), m.p.= 127–129°C; R_f = 0.64 (10:90 methanol/dichloromethane); ^{1}H-NMR (500 MHz, $CDCl_3$) δ ppm: δ 8.32 (s, 1H, N=C*H*), 7.46–6.73 (m, 6H, aromatic protons), 4.91 (s, 2H, Ph-CH_2), 3.88–3.81 (m, 12H, 4*OCH_3). ^{13}C-NMR (126 MHz, $CDCl_3$) δ 150.71, 149.65, 149.24, 148.41, 134.01, 133.90, 125.64, 123.73, 123.14, 122.25, 112.49, 111.30, 110.95, 110.52, 55.96, 55.93, 55.86, 55.80.

(E)-N-(3,4-dimethoxybenzyl)-1-(2-nitrophenyl) methanimine oxide (12)

Using the general procedure B, light yellow solid (2.8 g, 89%), m.p.= 161–163°C; R_f = 0.67 (10:90 methanol/dichloromethane); ^{1}H-NMR (500 MHz, $CDCl_3$) δ ppm: δ 9.07 (s, 1H, N=C*H*), 8.06–6.83 (m, 7H, aromatic protons), 5.02 (s, 2H, Ph-CH_2), 3.90 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3). ^{13}C-NMR (126 MHz, $CDCl_3$) δ 149.90, 149.33, 149.32, 133.40, 130.08, 129.46, 128.09, 124.95, 124.81, 124.44, 122.39, 112.39, 111.26, 72.20, 55.99, 55.94.

(E)-1-(3,4-dimethoxyphenyl)-N-(2-nitrobenzyl) methanimine oxide (13)

According to the general procedure B, light yellow solid (2.5 g, 79%), m.p.= 161–163°C; R_f = 0.5 (10:90 methanol/dichloromethane); ^{1}H-NMR (500 MHz, $CDCl_3$) δ ppm: 8.33 (s, 1H, N=C*H*), 8.18–6.85 (m, 7H, aromatic protons), 5.44 (s, 2H, Ph-CH_2), 3.91 (s, 6H, 2*OCH_3). ^{13}C-NMR (126 MHz, $CDCl_3$) δ 151.14, 148.50, 148.12, 134.04, 132.38, 129.74, 129.72, 128.84, 125.22, 123.67, 123.34, 111.06, 110.63, 66.99, 55.93, 55.89.

D. The Antibacterial and Antifungal Activity of the Synthesized Nitrones

The antibacterial and antifungal effects of the synthesized azomethine oxides (5-13) were evaluated by dissolving them in two different concentrations, 500 μg and 1000 μg, in 1 mL of dimethyl sulfoxide (DMSO). These concentrations were tested against Gram-positive *Staphylococcus aureus* bacteria and Gram-negative *Escherichia coli* bacteria, as well as their antifungal activity against *Candida albicans*. The agar-well diffusion method was employed to assess the antibacterial activity. Initially, Muller–Hinton agar was sterilized using an autoclave, then cooled to 50–55°C, and poured into petri dishes to form a uniform layer. Sterilized swabs were used to streak *S. aureus* and *E. coli* bacteria onto the agar surface, allowing them to solidify for 30 min. Subsequently, four wells with an 8 mm diameter were created in the agar layer, and 100 μL of each concentration of the prepared azomethine oxides, as well as dimethyl sulfoxide, levofloxacin, and clotrimazole (used as a standard drug for comparison), were added to the respective wells. The petri dishes were incubated at 37°C for 48 h, following which the diameter of the inhibitory zone was measured in millimeters.

III. Results and Discussion

The objective of this study is to produce new azomethine oxides through the transformation of specific substituted benzaldehydes into their corresponding hydroxylamines, as shown in Scheme 1 and Table I. Scheme 2 provides a general mechanism of the process for synthesizing phenylhydroxylamine derivatives (Mohammed, et al., 2023).

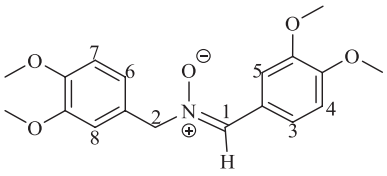
For the synthesis of azomethine oxides (5-13), a condensation strategy between *N*-phenylhydroxylamines and various substituted benzaldehydes was employed. This process is exemplified in Scheme 3 and summarized in Table II. Furthermore, Scheme 4 outlines the general mechanism involved in the synthesis of the desired compounds (Mohammed, et al., 2023)

The FT-IR spectra of the synthesized azomethine oxides clearly demonstrated that the carbonyl stretching band of the aldehyde disappeared, located between 1740 and –1720 cm^{-1}. Instead, new bands corresponding to (C=N), (C-N), and (N-O) vibrations appeared in the spectra within the following ranges: (1597–1583) cm^{-1}, (1346–1317) cm^{-1}, and (1112–1020) cm^{-1}, respectively.

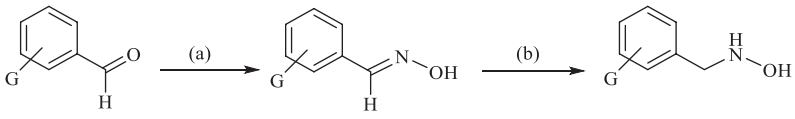
A. Determining the Configuration of Compound 11

Inouye's research findings indicate that the configuration of nitrones is influenced by the solvent used. Surprisingly, it has been observed that in non-polar solvents, *E*-configuration is the major product, whereas in polar solvents, *Z*-configuration is the major product (Inouye, 1980). Furthermore, the steric effect experienced by the *E*-isomer of azomethine oxide is lower compared to the *Z*-isomer, resulting in greater stability for the *E*-isomer (Figure 1). These results have been further supported by the findings of Qaddo and Abed, which align closely with Inouye's conclusions (Qaddo and Abed, 2022).

B. Determining the Configuration of 11 by ^{1}H-NMR



Compound 11's structure has been established using ^{1}H-NMR spectroscopy. It was emerged that the H at C-1 exhibited a singlet peak at 8.32 ppm, two protons at C-2



(1-4)

(a)= NaOH, H_2O, $NH_2OH.HCl$, HCl and CH_2Cl_2.
(b)= $NaBH_3CN$, MeOH, HCl-MeOH, KOH, H_2O and CH_2Cl_2

Scheme 1. General scheme of phenylhydroxylamine derivatives syntheses (**1-4**).

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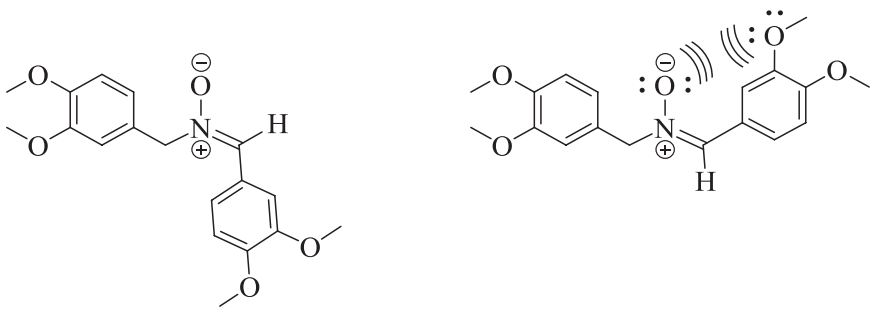
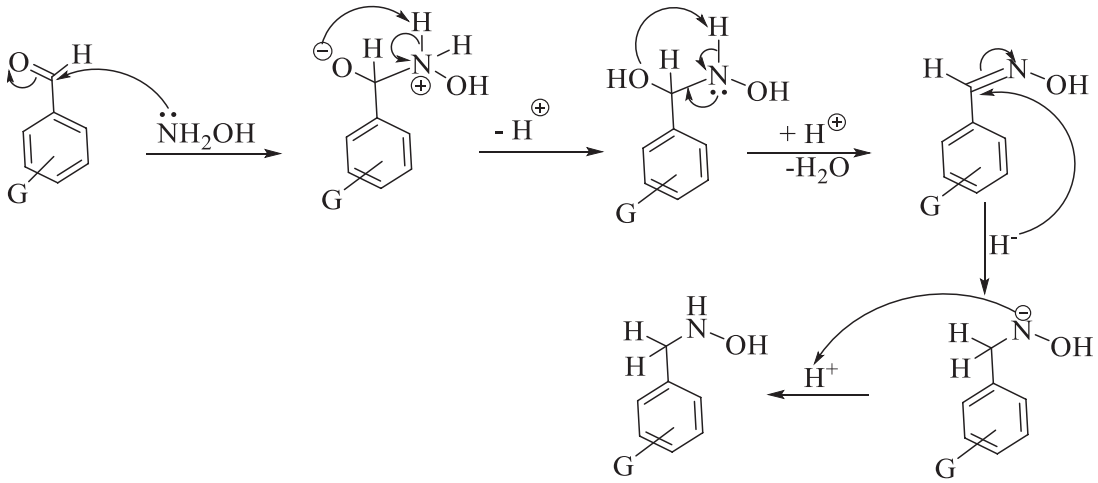
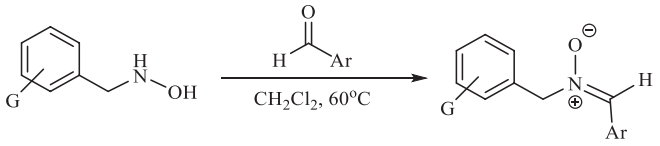


Fig. 1. *Z*-isomer and E-isomer azomethine oxide (Compound 11).



Scheme 2. General mechanism for the synthesis of phenylhydroxylamine derivatives (**1-4**).



Scheme 3. General scheme of azomethine oxide synthesis (**5-13**).

TABLE I
PHENYLHYDROXYLAMINE DERIVATIVES SYNTHESIS (1-4)

Entry	Product No.	Product Name	Yield %
Benzaldehyde	1	*N*-benzylhydroxylamine	94
3-methylbenzaldehyde	2	*N*-(3-methylbenzyl) hydroxylamine	96
3,4-dimethoxybenzaldehyde	3	*N*-(3,4-dimethoxybenzyl) hydroxylamine	96
2-nitrobenzaldehyde	4	*N*-(2-nitrobenzyl) hydroxylamine	93

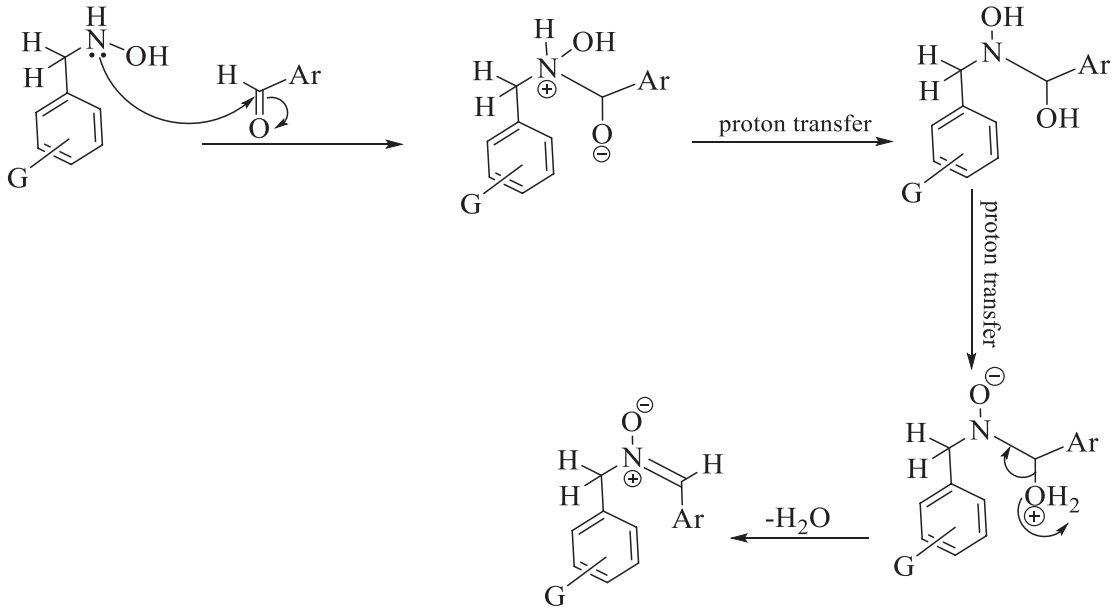
TABLE II
SYNTHESIS OF AZOMETHINE OXIDES (5-13)

N-phenylhydroxylamine derivative	Aldehyde	Azomethine oxide	Yield %
N-benzylhydroxylamine	3-methylbenzaldehyde	5	80
N-benzylhydroxylamine	3,4-dimethoxybenzaldehyde	6	89
N-(3-methylbenzyl) hydroxylamine	Benzaldehyde	7	88
N-(3-methylbenzyl) hydroxylamine	3-methylbenzaldehyde	8	92
N-(3-methylbenzyl) hydroxylamine	3,4-dimethoxybenzaldehyde	9	91
N-(3,4-dimethoxybenzyl) hydroxylamine	3-methylbenzaldehyde	10	91
N-(3,4-dimethoxybenzyl) hydroxylamine	3,4-dimethoxybenzaldehyde	11	91
N-(3,4-dimethoxybenzyl) hydroxylamine	2-nitrobenzaldehyde	12	89
N-(2-nitrobenzyl) hydroxylamine	3,4-dimethoxybenzaldehyde	13	79

appeared as a singlet at 4.91 ppm, and the aromatic protons of the phenyl group showed a multiplet from 7.46–6.73 ppm. Additionally, the protons of the methoxy groups appeared as a multiplet from 3.88–3.81 ppm. Furthermore, the ^{13}C-NMR analysis of this compound yielded the following results in ppm: 150.71, 149.65, 149.24, 148.41, 134.01, 133.90, 125.64, 123.73, 123.14, 122.25, 112.49, 111.30, 110.95, 110.52, 55.96, 55.93, 55.86, 55.80. The combined analysis of the ^{1}H-NMR and ^{13}C-NMR spectra provided strong confirmation of the correct structure of compound 11.

The confirmation of the configuration of compound 11 is crucial, as it serves as a vital reference point for determining the configuration of the remaining azomethine oxide compounds using only ^{1}H-NMR spectroscopy.

Table III presents the results of the study on the antibacterial and antifungal properties of synthetic



Scheme 4. General mechanism for the synthesis of azomethine oxides (**5-13**).

TABLE III
ANTIMICROBIAL ACTIVITY OF AZOMETHINE OXIDES (5-13)

Compound	Microorganism	500 µg/mL in 1 mL DMSO in mm	1000 µg/mL in 1 mL DMSO in mm
5.	*Escherichia coli*	NI	11
	Staphylococcus aureus	12	13
	Candida (Fungi)	13	15
6.	*Escherichia coli*	8	25
	Staphylococcus aureus	12	22
	Candida albicans	6	19
7.	*Escherichia coli*	7	15
	Staphylococcus aureus	11	15
	Candida albicans	NI	9
8.	*Escherichia coli*	NI	13
	Staphylococcus aureus	7	14
	Candida albicans	8	17
9.	*Escherichia coli*	7	15
	Staphylococcus aureus	10	15
	Candida albicans	8	11
10.	*Escherichia coli*	6	15
	Staphylococcus aureus	8	14
	Candida albicans	9	19
11.	*Escherichia coli*	NI	NI
	Staphylococcus aureus	NI	NI
	Candida (Fungi)	13	14
12.	*Escherichia coli*	11	12
	Staphylococcus aureus	NI	17
	Candida albicans	9	15
13.	*Escherichia coli*	9	17
	Staphylococcus aureus	11	20
	Candida albicans	13	25

Levofloxacin was effective against *E. coli* and *S. aureus*, with inhibition zones of 24 mm and 26 mm, respectively.
Clotrimazole was also effective against *C. albicans*, with an inhibition zone of 23 mm.
NI: No inhibition was observed

azomethine oxides against *C. albicans* fungus, *E. coli,* and *S. aureus* bacteria.

IV. Conclusion

To summarize, the structure of a synthetic azomethine oxide compound was confirmed through analysis of FT-IR, ^{1}H-NMR, and ^{13}C-NMR spectra. The experimental data validated the structure of this compound. In terms of biological activities, the synthesized azomethine oxides displayed remarkable antifungal properties against the *C. albicans* fungus, surpassing their antibacterial effects against *E. coli* and *S. aureus* bacteria.

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