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MOLECULAR DESIGN, SYNTHESIS, CHARACTERIZATION AND ANTIBACTERIAL EVALUATION OF (2E)-1-(CYCLOHEXYL(PHENYL)METHYLENE)-2-(2-METHOXYBENZYLIDENE) HYDRAZINE

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Abstract

The Schiff base derivatives have drawn a lot of interest in the field of medicinal chemistry due to their diverse biological activities and versatility in structure. In the current work, (2E)-1-(cyclohexyl(phenyl)methylene)-2-(2-methoxybenzylidene)hydrazine which is a hydrazone derivative of a Schiff base has been synthesized through condensation reaction of (Z)-(cyclohexyl(phenyl)methylene)hydrazine with 2-methoxybenzaldehyde under reflux conditions in ethanol. The product of the synthesis was obtained in 72 % yield and was obtained in the form of brown crystalline solid with a melting point of 178 °C. The ^{1}H NMR and FT-IR spectroscopic methods were used to confirm the molecular structure of the compound. The property of the synthesized compound as an antibacterial agent was tested against Staphylococcus aureus (Gram-positive) and Escherichia coli (Gram-negative) by the agar well diffusion technique. Ciprofloxacin was used as a positive control, whereas dimethyl sulfoxide (DMSO) served as the negative control. The compound formed had a moderate antibacterial activity with 14.0 ± 0.5 mm and 12.0 ± 0.6 mm being the inhibition zones with Staphylococcus aureus and Escherichia coli respectively. Comparatively, the standard antibiotic, ciprofloxacin, had larger areas of inhibition 26.0 ± 0.4 mm and 24.0 ± 0.5 mm, respectively, whereas the negative control did not have an antibacterial effect. The reason why the Gram-positive bacterium is slightly more susceptible to the activity could be the variation in the structural composition of bacterial cell walls. The findings indicate that the synthesized hydrazone derivative of

Schiff base has good antibacterial activity and could be used as a useful scaffold in designing new biologically active compounds.

1. INTRODUCTION

Schiff bases constitute an important class of organic compounds that contain the azomethine functional group (–C=N–), which is typically formed through a condensation reaction between primary amines or hydrazines and aldehydes or ketones [1]. Since their first discovery by the German chemist Hugo Schiff in the nineteenth century, these compounds have attracted significant attention in the fields of organic chemistry and medicinal chemistry [2-4]. The structural simplicity of Schiff bases, along with their ease of synthesis and wide structural diversity, makes them valuable intermediates in many chemical and biological applications. Over the past few decades, Schiff base derivatives have been extensively studied because of their wide range of biological and pharmacological properties [5]. Numerous reports have demonstrated that compounds containing the azomethine linkage exhibit antibacterial, antifungal, antiviral, anti-inflammatory, antioxidant, and anticancer activities [6]. The biological activity of Schiff bases is often associated with the presence of the imine (C=N) functional group, which plays an essential role in their interaction with biological systems [7-9]. The azomethine linkage can participate in hydrogen bonding, coordinate with metal ions, or interact with enzymes and other biomolecules present in microbial cells [10]. Such interactions may disrupt essential metabolic pathways in microorganisms, ultimately leading to inhibition of bacterial growth. In addition to the imine functionality, the biological behavior of Schiff base compounds is strongly influenced by the presence of various substituents attached to the aromatic or aliphatic framework of the molecule. Functional groups such as hydroxyl, methoxy, halogens, and heterocyclic moieties are known to modify the electronic distribution and lipophilicity of the molecule, thereby affecting its interaction with biological targets [11-15].

In recent years, the search for new antimicrobial agents has become increasingly important due to the rapid emergence of antibiotic-resistant microorganisms [16-18]. The widespread and often uncontrolled use of antibiotics has led to the development of bacterial strains that are resistant to many commonly used drugs. As a result, infections caused by resistant bacteria have become a serious concern for public health worldwide. Pathogenic bacteria such as *Staphylococcus aureus* and *Escherichia coli* are frequently associated with a variety of human diseases. *Staphylococcus aureus*, a Gram-positive bacterium, is responsible for numerous infections including skin and soft tissue infections, pneumonia, and bloodstream infections [19-23]. On the other hand, *Escherichia coli*, which belongs to the Gram-negative group of bacteria, is widely known for causing urinary tract infections, gastrointestinal disorders, and other opportunistic infections [24]. Because of the structural differences between Gram-positive and Gram-negative bacteria cell walls, the effectiveness of antibacterial agents can vary significantly [25, 26]. Therefore, the development of new compounds capable of inhibiting the growth of these microorganisms remains an important objective in medicinal chemistry [27]. Among various classes of biologically active compounds, Schiff base derivatives have been widely investigated for their antimicrobial potential. Several studies have reported that Schiff bases containing aromatic rings and heteroatoms exhibit enhanced antibacterial activity due to improved electron delocalization and increased molecular stability [28-31]. The presence of conjugated systems within these molecules can facilitate interactions with bacterial proteins and nucleic acids, which may lead to disruption of essential cellular functions [32-36]. Moreover, structural modifications in Schiff base molecules, such as the introduction of electron-donating or electron-withdrawing substituents, have been shown to significantly influence their antimicrobial effectiveness [37-41].

Hydrazone-based Schiff bases represent a particularly interesting subclass of these compounds. Hydrazones contain both the

azomethine (C=N) linkage and additional nitrogen donor atoms that can participate in hydrogen bonding and coordination interactions with biological molecules [42-44]. Because of these structural features, hydrazone derivatives have been widely explored for their pharmacological properties. Previous investigations have shown that hydrazone compounds possess diverse biological activities, including antibacterial, antifungal, antitubercular, and anticancer effects [45]. The incorporation of aromatic rings in hydrazone structures can further enhance their biological activity by increasing their ability to interact with biomolecules through π–π stacking interactions and hydrophobic forces [46-49]. Compounds containing cyclohexyl and phenyl substituents are also of particular interest in medicinal chemistry because the presence of both aliphatic and aromatic groups may influence the physicochemical and biological properties of the resulting molecules [50]. The cyclohexyl moiety contributes to the hydrophobic character of the compound, which may facilitate its penetration through lipid membranes of bacterial cells. Meanwhile, the phenyl ring can stabilize the azomethine linkage through conjugation and electronic interactions [51-53]. Furthermore, the introduction of methoxy-substituted aromatic aldehydes into the molecular framework may alter the electronic properties of the compound, potentially improving its biological activity and stability [54-57].

The structural characterization of Schiff base derivatives is commonly carried out using spectroscopic techniques such as Fourier Transform Infrared (FT-IR) spectroscopy and proton nuclear magnetic resonance (^{1}H NMR) spectroscopy. These analytical methods provide valuable information about the functional groups and structural features of synthesized compounds. For instance, the formation of the azomethine bond can be confirmed by the appearance of characteristic absorption bands in the FT-IR spectrum as well as by the presence of distinctive imine proton signals in the ^{1}H NMR spectrum. Such spectroscopic analyses play an essential role in verifying the successful synthesis of Schiff base compounds. Considering the wide range of biological activities associated with hydrazone-based Schiff bases and the continuing need for new antimicrobial agents, the synthesis and biological evaluation of novel derivatives remain an active area of research [58-60].

In the present study, a novel hydrazone Schiff base derivative, (2E)-1-(cyclohexyl(phenyl)methylene)-2-(2-methoxybenzylidene)hydrazine**,** was synthesized through a condensation reaction between *(Z)-(cyclohexyl(phenyl)methylene)hydrazine* and *2-methoxybenzaldehyde*. The synthesized compound was characterized using spectroscopic techniques including ^{1}H NMR and FT-IR spectroscopy in order to confirm its molecular structure. In addition, the antibacterial activity of the synthesized compound was evaluated against two representative bacterial strains, *Staphylococcus aureus* and *Escherichia coli*, using the agar well diffusion method. The antibacterial effectiveness of the compound was compared with that of the standard antibiotic ciprofloxacin**,** while dimethyl sulfoxide (DMSO) was used as the negative control. The results obtained from this study also provide useful insights into the antibacterial potential of hydrazone-based Schiff base derivatives and could contribute to the development of new compounds with possible pharmaceutical applications.

2. EXPERIMENTAL

2.1. Material and instruments

In this work, analytical grade reagents and solvent were used. Ethanol, potassium carbonate and the various acid halides were used as chemicals and reagents. Purities in the products were analyzed through TLC cards that were impregnated with silica. All reactions were set with n-Hexane and ethyl acetate as the solvent systems as the TLC profiles. The determination of the time needed by the reaction to yield the excellent product was carried out through TLC. The visualization of spots on the TLC strips was done using the UV lamp so as to have pure product. Borosilicate and Pyrex clean and dry glassware were used to achieve pure product. All the reactions were carried out in accordance with the definite protocol. Synthesis of the cyclohexyl phenyl ketone bis Schiff base derivatives was done using standard procedures. The synthetic grade

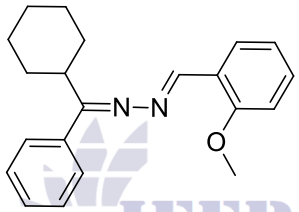
reagent and solvents used all were purchased from Merck, Aldrich and BDH. The synthesized compound was characterized by FT-IR and proton NMR spectrophotometer (Schimadzu-1802 Japan) and Bruker (Advance III MHz) spectrometer.

2.2. Synthesis of (*2E*)-1-(cyclohexyl(phenyl)methylene)-2-(2-methoxybenzylidene)hydrazine

The (Z)-(cyclohexyl(phenyl)methylene)hydrazine (0.1196 mmol (0.383 g) was added to ethanol in a round bottom flask and stirred with a hotplate. Few drops of acetic acid and an equal quantity of 2-methoxybenzaldehyde were added to the round bottom flask after 15 minutes. The solution obtained was refluxed at 70 °C for 10 hours. To check the progress of reaction TLC was taken in *n*-hexane ethyl acetate solvent system. After reaction completion the product formed was precipitated in cold water, filtered and dried.

Physical data

Molecular formula	$C_{21}H_{24}N_2O$
Molecular Weight	320.43 g/mol
Color	Brown
Solubility	Chloroform, DMSO, DMF
Melting point	178 °C
Yield	72%



(2*E*)-1-(cyclohexyl(phenyl)methylene)-2-(2-methoxybenzylidene)hydrazine

158

^{1}HNMR (CD_3Cl, 400Hz, δ(ppm): δ = 1.99-1.64 (m, 5H, CH_2-Cyclic), δ = 1.61-1.14 (m, 5H, CH_2-Cyclic), δ =3.26 (tt, *J* = 11.5 Hz, 3.3 Hz, 1H, -CH-Cyclic), δ =3.89 (s, 3H, CH_3-O-Ar), δ=8.12 (dd, *J*= 7.7 Hz, 1.8 Hz, 1H, Ar-H), δ =7.96-7.87 (m, 2H, Ar-H), δ =7.63-7.19 (m, 3H, Ar-H), 7.12-6.76 (m, 3H, Ar-H), δ =9.09 (s, 1H, Ar-CH=N-).

2.3. Antibacterial Activity

The antibacterial activity of the synthesized Schiff base compound (2E)-1-(cyclohexyl(phenyl)methylene)-2-(2-methoxybenzylidene)hydrazine was evaluated against two bacterial strains, *Escherichia coli* (Gram-negative) and *Staphylococcus aureus* (Gram-positive), using the agar well diffusion method. The reason why these bacterial strains were chosen is that they are typical representatives of pathogenic microorganisms that are involved in the initial screening with antimicrobial agents. The bacterial cultures were obtained from microbiology laboratory and kept in nutrient agar medium. The inoculum of each bacterial strain was freshly prepared by transferring a loopful of bacterial culture to sterile nutrient broth and then left to incubate at 37 °C in the same condition of 18-24 hours. Turbidity of the bacterial suspension was also adjusted to about 0.5 McFarland standard so as to achieve a homogenous bacterial population. Bacteria suspension was uniformly spread on sterile nutrient agar plates using sterile cotton swab inoculation. The sterile cork borer was used to make wells in the agar plates with dimensions of about 6 mm in diameter. To obtain the test solution, the synthesized compound (158) was dissolved in dimethyl sulfoxide (DMSO). 50 µL of the test solution was added to each of the wells with caution. The positive control (standard antibacterial drug) was ciprofloxacin and the negative control was DMSO to ensure that the

solvent itself did not have an inhibitory impact on the growth of bacteria. It was left standing about 30 minutes to allow the diffusion of the compound into the agar medium and then incubated at 37 0 C in 24 hours. An analysis of antibacterial activity was done after incubation by measuring the diameter of the zone of inhibition (mm) around each well with a digital caliper. The experiments were conducted in triplicate and then the average values were reported.

3. Results and Discussion

3.1. Characterization

3.1.1. ^{1}HNMR

The ^{1}HNMR spectrum of the Compound (2E)-1-(cyclohexyl(phenyl)methylene)-2-(2-methoxybenzylidene)hydrazine shown in Figure 1 indicates that there are two multiplets between 1.99 and 1.14 with an integral ratio of 5H, 5H and triplet of triplet of integral ratio of 1H at 3.24 were corresponding to the cyclohexy ring. There were 3 Multiplets observed between 7.97 and 6.76 with integral ratio 2H, 3H, 3H, and a duplet of duplet at 8.12 with an integral ratio 1H which was attributed to the two aromatic ring protons. The methoxy group attached to aromatic ring was equated to a singlet at 3H which had an integral ratio 3H and the imine proton was equated to a singlet at 9.09 of integral ratio 1H.

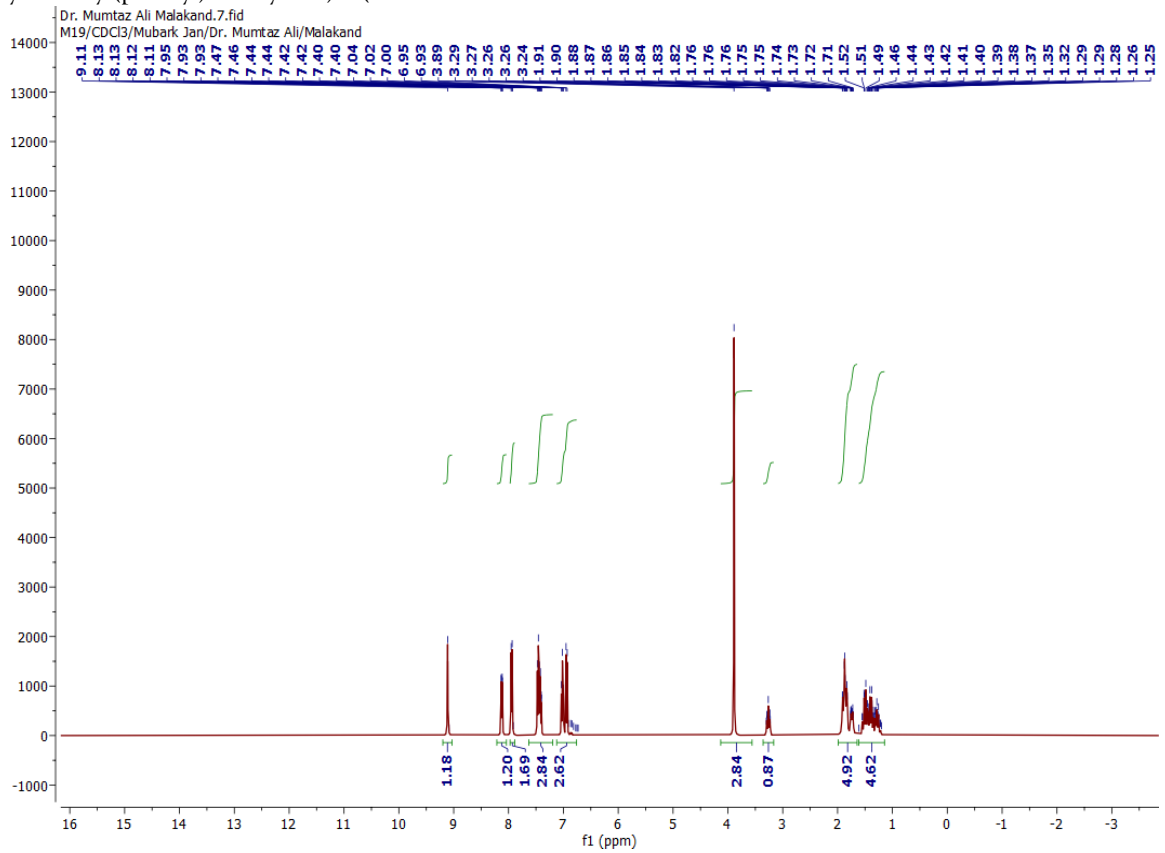


Figure 1: ^{1}HNMR Spectrum of (2E)-1-(cyclohexyl(phenyl)methylene)-2-(2-methoxybenzylidene) hydrazine

3.1.2. FT-IR

In Figure 2 the FT-IR spectrum of the compound (2E)-1-(cyclohexyl(phenyl)methylene)-2-(2-methoxybenzylidene) hydrazine is shown, confirms the successful synthesis of the synthesized Schiff base derivative. This is mainly supported by the presence of two characteristic absorption bands observed at 1615 cm^{-1} and 1666 cm^{-1}, which correspond to the stretching vibrations of the imine (C=N) functional groups present in the molecule. The appearance of these bands is consistent with the formation of the azomethine linkage expected in the synthesized compound. In addition, the absorption bands observed in the range of 2842–2930 cm^{-1} correspond to the aliphatic C–H stretching vibrations of the

cyclohexyl ring, while the bands appearing between 1438 and 1208 cm^{-1} can be attributed to the bending vibrations of aliphatic C–H bonds. The spectrum also shows absorption bands in the region of 3020–3180 cm^{-1}, which are characteristic of aromatic C–H stretching vibrations, whereas the bands between 1024 and 701 cm^{-1} are associated with the bending vibrations of aromatic C–H bonds.

Generally, carbonyl compounds exhibit strong stretching absorption bands above 1700 cm^{-1}, whereas the stretching vibrations of the imine (C=N) functional group typically appear at slightly lower frequencies, usually below 1660 cm^{-1}. It is also well established that the exact position of the C=N stretching band depends on the nature of the substituents attached to the imine group (R_1–C=N–R_2). For example, when both substituents are saturated alkyl groups, the stretching frequency of the C=N bond usually appears in the range of 1664–1672 cm^{-1}. However, when the substituents are unsaturated groups such as aromatic rings or phenyl moieties, conjugation with the imine bond occurs, which results in a shift of the stretching frequency toward lower wavenumbers, sometimes extending down to approximately 1400 cm^{-1}. This shift is mainly attributed to the delocalization of electrons within the conjugated system, which reduces the effective bond order of the imine linkage.

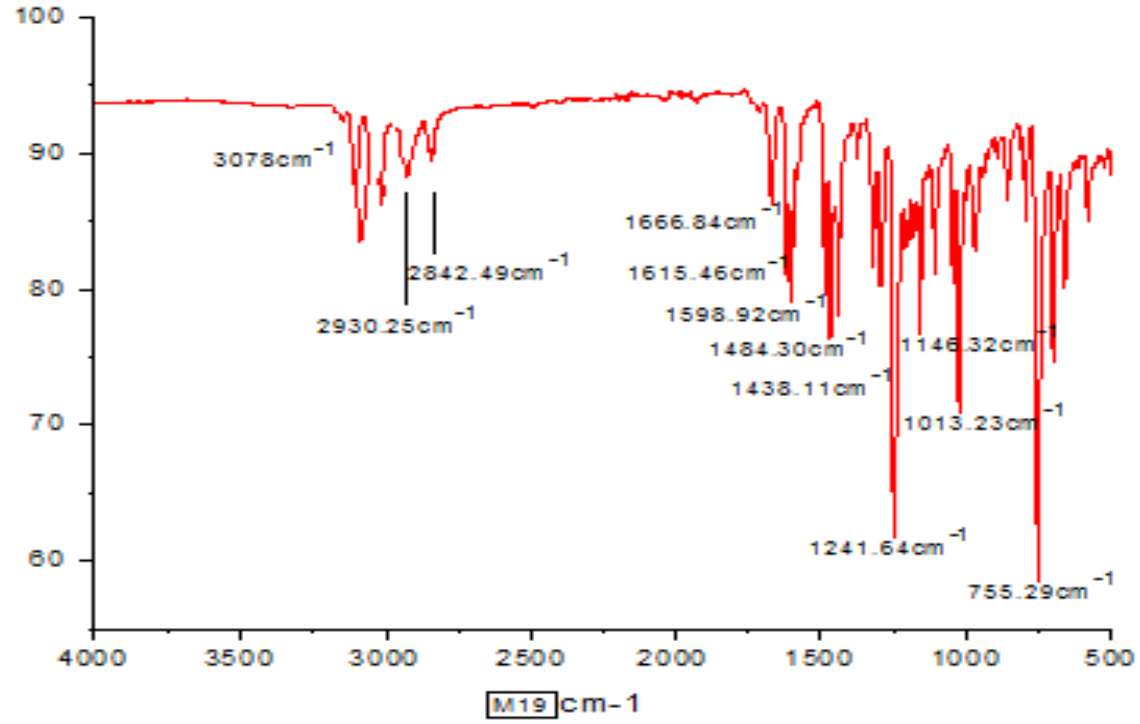
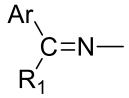
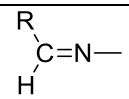
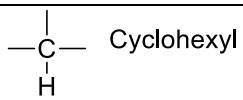


Figure 2: FT-IR Spectrum of (2E)-1-(cyclohexyl(phenyl)methylene)-2-(2-methoxybenzylidene) hydrazine

Table 1: FT-IR Spectral data of **(2E)-1-(cyclohexyl(phenyl)methylene)-2-(2-methoxybenzylidene) hydrazine**

Functional group	Stretching frequency (υ)	Bending frequency (υ)
	1615	.....
	1666	.....
	2842-2930	1438-1208

H–Ar	3020-3180	1024-701

Antibacterial Activity

The antibacterial activity of the synthesized Schiff base compound (2E)-1-(cyclohexyl(phenyl)methylene)-2-(2-methoxybenzylidene) hydrazine was investigated against *Staphylococcus aureus* and *Escherichia coli* using the agar well diffusion method. The results indicate that the compound showed moderate antibacterial activity against both bacterial strains as compared to the standard drug. The compound gave a zone of inhibition of 14 mm in the case of Staphylococcus aureus and 12 mm in the case of Escherichia coli. As compared to this synthesized Schiff base the standard antibiotic, ciprofloxacin showed much greater zones of inhibition of 26 mm and 24 mm against Staphylococcus aureus and Escherichia coli, respectively. The negative control DMSO showed no inhibition zone, confirming that the observed antibacterial activity resulted from the synthesized Schiff base and not from the solvent.

The antibacterial activity of the synthesized (2E)-1-(cyclohexyl(phenyl)methylene)-2-(2-methoxybenzylidene) hydrazine being slightly stronger against the Gram-positive bacterium Staphylococcus aureus than the Gram-negative bacterium Escherichia coli can be explained by the differences in cell wall structures of the bacteria. The gram-negative bacteria also have an outer membrane that is characterized by lipopolysaccharides that serve as a protective layer and minimize the permeability of many antimicrobial agents. The presence of the azomethine (C=N) functional group that has been associated to play a significant role in the biological activity of Schiff base derivatives is also likely to be related to the observed antibacterial activity. Moreover, it is also possible that aromatic rings and methoxy substituent found in the structure make the molecule more lipophilic and therefore, more capable of interacting with bacterial cell membranes and intracellular targets. These results show that (2E)-1-(cyclohexyl(phenyl)methylene)-2-(2-methoxybenzylidene) hydrazine have moderate antibacterial potential, although its activity is lower than that of the standard antibiotic. These findings also suggest the Schiff base derivatives of this type could serve as promising candidates for further structural modification and biological investigation.

Table: 2 Antibacterial activity of the synthesized Schiff base compound 2E)-1-(cyclohexyl(phenyl)methylene)-2-(2-methoxybenzylidene)hydrazine compared with standard drug Ciprofloxacin

S.No	Sample	Bacterial Strain	Zone of Inhibition (mm) (Mean ± SD)
1	Compound	Staphylococcus aureus	14.0 ± 0.5
2	Compound	Escherichia coli	12.0 ± 0.6
3	Ciprofloxacin (Standard)	Staphylococcus aureus	26.0 ± 0.4
4	Ciprofloxacin (Standard)	Escherichia coli	24.0 ± 0.5
5	DMSO (Negative Control)	Staphylococcus aureus	0.0 ± 0.0
6	DMSO (Negative Control)	Escherichia coli	0.0 ± 0.0

Conclusion

In the present study, a novel hydrazone based Schiff base derivative, (2E)-1, (cyclohexyl(phenyl)methylene)-2,(2-methoxybenzylidene)hydrazine was synthesized through condensation of (Z)-(cyclohexyl(phenyl)methylene)hydrazine and 2-methoxybenzaldehyde. The synthesized (2E)-1, (cyclohexyl(phenyl)methylene)-2,(2-methoxybenzylidene)hydrazine obtained in high yield and it characterization was done FT-IR and ^{1}H NMR spectroscopy methods through which the formation of the intended azomethine functional groups, as well as the structure of the compound was established. Agar well diffusion test was used to determine

the antibacterial potential of the synthesized compound against two bacterial strains representative of Staphylococcus aureus and Escherichia coli. The compound showed moderate antimicrobial properties, as they formed quantifiable inhibition areas with both of the tested microorganisms. Even though it's antibacterial activity was not as effective as the standard antibiotic ciprofloxacin, the compound still demonstrated some appreciable inhibitory properties especially on Gram-positive bacterium Staphylococcus aureus. The negative control which lacked antibacterial activity served to ensure that the inhibition was caused by the synthesized compound itself. The results of the observed antibacterial activity could be explained by the presence of the azomethine (C=N) functional group, as well as the aromatic and methoxy substituents in the molecule structure, which could potentially contribute to the interactions with the microbial cells. The mentioned structural characteristics have the potential to enhance lipophilicity and assist in the penetration of the compound through the bacterial membranes. In general, these findings show that hydrazone-based Schiff base analogs are promising molecular scaffolds of the construction of novel antimicrobial agonists. The further research with structural modification and forming metal complex and comparing it with the wider variety of microbial strains can give a better understanding of their biological possibilities and the potential use in pharmaceutical practice.

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