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The Search for Extraterrestrial Life Through Chemistry

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Abstract

In this work, a novel hydrazone Schiff base, (2E)-1-(cyclohexyl(phenyl)methylene)-2-(4-chlorobenzylidene)hydrazine was synthesized successfully with the help of a stepwise condensation procedure and was characterized with the help of spectroscopic analysis. The synthesized compound was identified by the structure through FT-IR and the use of the 1H NMR spectroscopy which identified the typical azomethine (C=N) stretching vibrations and proton signal in line with the proposed structure. The two conjugated imine linkages, aromatic rings and a cyclohexyl moiety presence improves the structural rigidity, conjugation and lipophilicity. The agar disc diffusion and the broth microdilution techniques were used to determine the antibacterial activity of the compound against Klebsiella pneumoniae. The compound showed concentration dependent antimicrobial activity, with the highest zone of inhibition being 12.2 ± 0.4 mm at 8.0 mg/mL and minimum inhibitory concentration (MIC) is being 2.0 mg/mL. The observed anti-bacterial efficacy is attributed to the joint action of the azomethine functional groups and the chloro-substituted aromatic ring, which promote the membrane penetration and interfere with the bacterial metabolism. These results suggest that the synthesized hydrazone Schiff base represents a promising scaffold for the development new antibacterial agents against Gram-negative bacteria.

Keywords: *Schiff Base, Hydrazine, FT-IR, 1H NMR, Klebsiella, Antibacterial Activity*

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1. INTRODUCTION

The Schiff bases and hydrazone derivatives form a significant family of organic compounds that is formed by the condensation reaction of carbonyl compounds and primary amines or hydrazines to form the typical azomethine (–C=N–) functional group [1]. They have continued to draw both interest in organic and medicinal chemistry as well as coordination chemistry because of their ease of synthesis, structural versatility and tunable physicochemical characteristics. The imine linkage allows the delocalization of electrons to occur efficiently and the nitrogen donor atoms also provide strong sites of coordination hence, Schiff bases can be utilized in numerous chemical and biological processes [2-4]. Schiff bases that incorporate hydrazone groups are of particular interest due to the fact that they have two centers of nitrogen donation, which contribute to conjugation and stabilization of the molecular structure by the resonance effect. This long conjugation enhances rigidity and conduct of the molecules throughout the structure which affects reactivity and intermolecular interactions [5]. The π-electron delocalization of hydrazones is further increased by introduction of aromatic rings, and addition of alicyclic groups like cyclohexyl groups provides steric bulk and conformational stability. These structural components in combination make it possible to fine tune the molecular geometry, lipophilicity, and electronic distribution, which are the factors that govern the chemical behavior of the derivatives of Schiff bases [6]. The arylalkylketone derivatives of the hydrazone Schiff base, as well as the substituent aromatic aldehyde derivatives, are of interest in particular because they are highly conjugated and possess well-defined stereochemistry. This (2E)-1-(cyclohexyl(phenyl)methylene)-2-(4-chlorobenzylidene) hydrazine is a structurally different hydrazone Schiff base prepared using a stepwise condensation method [7-10]. The molecule has two azomethine linkages that are conjugated with the phenyl and 4-chlorophenyl rings, as well as a cyclohexyl group, which gives the molecule hydrophobic properties and structural rigidity. E-configuration of the imine bond allows the molecules to become planar allowing the mutual orbital overlap and intramolecular stabilization. Replacement of aromatic rings by halogen has a considerable role in the electronic and steric modification of the Schiff base. Specifically, chloro substituents have the effect of an electron-withdrawing inductive effect and resonance interactions within the aromatic system are preserved. This two-fold effect changes the distribution of electron density throughout the azomethine connectivity and it may increase intermolecular interactions. Also, it has been observed that halogenated aromatic systems enhance the molecular lipophilicity that can affect solubility, membrane permeability and general chemical reactivity. The addition of a 4-chlorophenyl group to the current compound is thus a factor that influences the unique electronic and structural properties of the compound [11, 12]. The spectroscopic characterization would be necessary to ensure the successful creation of hydrazone Schiff bases and explain their structural peculiarities. The FT-IR spectroscopy offers useful data about the creation of the azomethine bonds based on the presence of the characteristic C=N stretching vibrations, and the assignment of all aliphatic, aromatic, and imine protons is possible with the help of the 1H NMR spectroscopy [13-18]. A combination of these methods provides solid evidence to the suggested molecular structure and stereochemistry. This type of characterization is especially significant to conjugated systems, where any fine variation in electronic environment can have a strong impact on spectral behavior. Schiff bases and hydrazone

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derivatives have acquired more and more popularity in the recent years because of their potential to be applied in biology, especially in the antimicrobial field [19-24]. The identified problem of antimicrobial resistance all over the world has led to the increased efforts aimed at discovering new chemical compounds that could be used against the microorganisms that cannot be addressed through the existing drugs. Gram negative bacteria, including Klebsiella pneumoniae can be very challenging as they have complex cell wall structure and built-in resistance mechanisms that inhibit the efficacy of most standard antibiotics. The compounds that had been found to overcome these barriers include those with longer conjugation, heteroatoms, and hydrophilic domains [25-30]. As noted in earlier research, hydrazone Schiff bases containing aromatic and halogenated functional groups have been found to be superiorly active biologically, which is explained by enhanced beta 2 binding to bacterial enzymes and cell membranes [31-34]. It is thought that the presence of azomethine groups disrupts the key bacterial metabolic activity whereas the hydrophobic moieties promote penetration by means of lipid-rich membranes [35-39]. These results indicate the role of rational molecular designing in synthesis of new antibacterial candidates using Schiff base structures [40-42]. In this paper, the synthesis and the overall spectroscopic characterization of (2E)-1-cyclohexyl(phenyl)methylene)-2-4-chlorobenzylidene)hydrazine are reported. Also, the antibacterial effect of the synthesized compound was assessed against Klebsiella pneumoniae by the means of standard agar disc diffusion and broth microdilution tests. The findings are provided in relation to the structural characteristics of the compound and to the literature-reported hydrazone Schiff bases, which allows obtaining understanding of the structure and activity relationships as well as the prospects of using this type of compounds in the further development.

2. EXPERIMENTAL

2.1. Materials and Instruments

Analytical grade reagents and solvent was used in this work. The chemicals and reagents that were used included ethanol, potassium carbonate and various acid halides. The purities of the products were analyzed using the TLC cards impregnated with silica. TLCs of every reaction were developed by the use of n-Hexane and ethyl acetate as a solvent system. The time of the completion of the reaction in order to arrive at the maximum yield of the product was determined using TLC. Visualization of the spots on the TLC strips was done with the UV lamp. Pyrex and borosilicate glasses were cleaned and dried in order to get pure product. The grade reagents were high purity chemicals and synthetic grade; all the reactions were conducted as per the definite protocol. Synthetic grade reagent and solvents obtained are all of the Merck, Aldrich and BDH. FT-IR and proton NMR characterization of the synthesized compound was done using FT-IR spectrophotometer (Schimadzu-1802 Japan) and Bruker (Advance III MHz) spectrometer.

2.2.Synthesis of (Z) (cyclohexyl(phenyl)methylene)hydrazine as precursor

A solution of ethanol (as a solvent) was added to the hydroxyl phenyl cyclohexyl ketone and drops of glacial acetic acid were added to the solution after which it was stirreded at 80ºC temperature and in the presence of hydrazine hydrate. Supervision of the reaction was done by TLC in n-hexane ethyl acetate solvent system and product that was formed after the reaction was precipitated in cold water, filtered and dried.

2.3.Synthesis of (*2E*)-1-(cyclohexyl(phenyl)methylene)-2-(4 chlorobenzylidene)hydrazine

Weighted 0.1196 mmol (0.038 g) of (Z)-(cyclohexyl(phenyl)methylene)hydrazine in

round bottom flask and stirred it on a hotplate in

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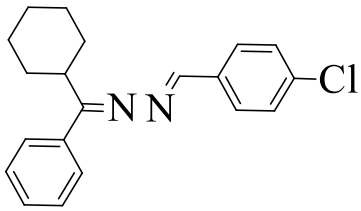
ethanol. Few drops of glacial acetic acid and 4-chlorobenzaldehyde were stirred with the round bottom flask after 15 minutes. The flask containing the resulting solution was refluxed at 70°C and allowed to remain overnight. The progress of the reactions was monitored with the help of different solvent system of ethyl acetate and n-hexane. The product that was formed after the reaction was precipitated in cold water and filtered and dried.

Molecular formula	**$C_{20}H_{21}N_2Cl$**
Molecular Weight:	**324.85 g/mol**
Color	**White**
Solubility	**Chloroform, DMSO, DMF**
Melting point	**170 °C**
Yield	**82%**

Physical data



(1*E*)-1-(4-chlorobenzylidene)-2-(cyclohexyl(phenyl)methylene)hydrazine

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2.4. Characterization

^{1}HNMR (CD_3Cl, 400Hz, δ(ppm): δ=1.27-0.84 (m, 5H, CH_2-Cyclic), δ=1.70-1.33 (m, 5H, CH_2-Cyclic), δ=2.23 (ddd, J=14.04 Hz, 9.4 Hz, 3.1 Hz, 1H, 1CH-Cyclic), δ =7.25-7.11 (m, 4H, H-Ar), δ =7.66-7.21 (m, 4H, Ar-H) δ=7.01-6.91 (m, 1H, Ar-H), δ=8.59 (s, 1H, Ar-CH=N-). FT-IR data of the compound (*2E*)-1-(cyclohexyl(phenyl)methylene)-2(4chlorobenzylidene)hydrazine given in Table 1.

2.5. Antibacterial Activity

The antibacterial activity of (2E)-1-(cyclohexyl(phenyl)methylene)-2-(4-chlorobenzylidene) hydrazine was assessed using conventional agar disc diffusion and broth microdilution technique against the Klebsiella pneumoniae. The bacterial strain was grown at 37°C on Mueller-Hinton agar. A fresh bacterial suspension equal to 0.5 McFarland standard was used in each experiment after the dilution of the substance in DMSO to 0.5 8.0 mg/mL making a stock solution (10 mg/mL). Agar plates previously inoculated with the bacterial culture were covered by 6 mm filter paper discs impregnated with 10 µL of the different concentrations and sterile. The negative control was DMSO and the positive control was gentamicin (10 µg/disc). The areas of inhibition were recorded in millimeters following the incubation of plates at 37°C in 18-24 hours. Minimal concentration of the broth microdilution was calculated using the broth microdilution method. The lowest concentration with no visible bacterial growth was observed as the minimum inhibitory concentration (MIC) after 18 hours of incubating at 37°C.

3. Results and Discussion

3.1. Characterization

a) ^{1}HNMR

Fig 1 shows the 1HNMR spectrum of the (2E)-1(cyclohexyl(phenyl)methylene)-2(4-chlorobenzylidene)-hydrazine, which contained two multiplets of 5H, 5H in the range 1.70-0.84, and three multiplets of triplet 2.36 of integral ratio 1H. The two aromatic ring protons were observed to have three Multiplet peaks at 7.67 to 6.91 of integral ratio 4H, 4H and 1H and the imine proton was observed at 8.46 of integral ratio 1H.

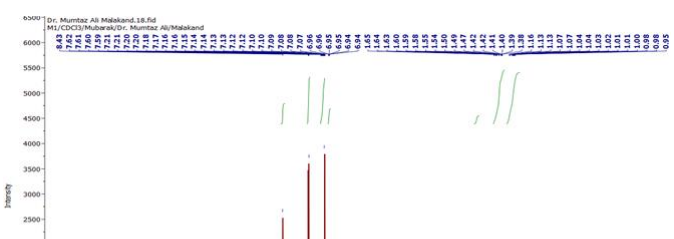

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Figure1: [1]HNMR Spectrum of compound (*2E*)-1-(cyclohexyl(phenyl)methylene)-2-(4-chlorobenzylidene)hydrazine

b) FT-IR

The FT-IR spectrum of the compound (Figure 2) confirms the successful synthesis of the target molecule. This is evidenced by the presence of two characteristic absorption bands at 1595 and 1625 cm^{-1}, which are attributed to the stretching vibrations of two imine (C=N) bonds present in the structure. The absorption bands observed in the range of 2950–2850 cm^{-1} correspond to aliphatic C–H stretching vibrations, while those appearing between 1401 and 1341 cm^{-1} are assigned to C–H bending vibrations of the cyclohexyl ring. In addition, the bands detected between 3130 and 3030 cm^{-1} are due to aromatic C–H stretching vibrations, and the bands in the region of 1095–825 cm^{-1} arise from aromatic C–H bending modes. Typically, carbonyl compounds exhibit stretching vibrations above 1700 cm^{-1}, whereas imine (C=N) stretching vibrations occur at lower frequencies, generally below 1660 cm^{-1}. It is also well established that the infrared stretching frequency of the C=N bond depends on the nature of the substituents attached to it (R^1–C=N–R^2). For imines containing saturated alkyl groups, the C=N stretching frequency usually appears in the range of 1664–1672 cm^{-1}. However, when the imine group is conjugated with unsaturated alkyl or phenyl substituents, the stretching frequency shifts to lower wavenumbers, in some cases approaching 1400 cm^{-1}, due to the effect of conjugation.

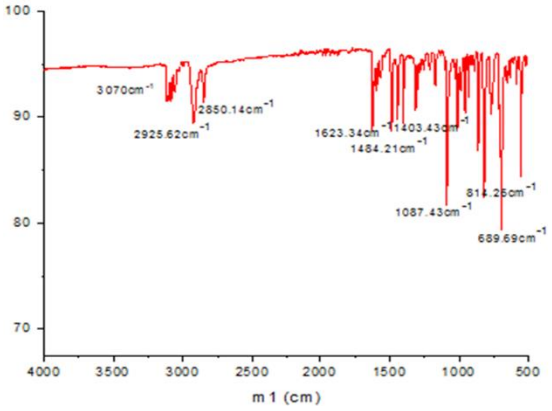

Figure 2: FT-IR Spectrum of compound(*2E*)-1-(cyclohexyl(phenyl)methylene)-2-(4-chlorobenzylidene) hydrazine **Table 1:** FT-IR Spectral data of compound

Functional group	Stretching frequency (υ)	Bending frequency (υ)
Ar, C=N—, R_1	1595	……
R, C=N—, H	1625	……
—C— Cyclohexyl, H	2950-2850	1401-1312
H−Ar	3140-3030	1095-825

Antibacterial Activity

The synthesized Schiff base exhibited strong antibacterial activity towards Klebsiella pneumoniae. The antibacterial effect of the compound was evidently proportional to concentration. The highest concentration of 8.0mg/mL exhibited a zone of inhibition of 12.2 + 0.4 mm but at lower concentrations of 4.0 and 2.0mg/mL a zone of inhibition of 9.7 + 0.6mm and 7.5 + 0.5mm was discovered respectively. DMSO did not show inhibitory effect whereas gentamicin produced a zone of

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inhibition of 22.5 + 0.5 mm. The lowest inhibitory concentration (MIC) of the compound to Klebsiella pneumoniae was established as 2.0mg/mL, indicating good growth inhibition at a medium level. The present results are in line with the earlier available hydrazone and Schiff derivative of halogenated aromatic rings that in most cases possess a MIC of 1-4 mg/mL against Gram negative bacteria. The antibacterial action of the compound is caused by the azomethine (-C=N -) group that is known to destabilize bacterial enzymatic systems and the chloro-substituted phenyl ring, which increases the lipophilicity of the compound and facilitates its penetration into the outer membrane of Klebsiella. Moreover, the cyclohexyl and phenyl groups can improve hydrophobic interactions between them and the bacterial cell wall leading to growth arrest and membrane destabilization. Overall, the observed inhibition zones and minimum inhibitory concentration (MIC) values verify that (2E)-1-(cyclohexyl(phenyl)methylene)-2-(4-chlorobenzylidene)hydrazine has moderate to good antibacterial activity against Klebsiella pneumoniae, which is similar to similar compounds reported in the literature.

Table 2. Zone of Inhibition of *Klebsiella pneumoniae* by the Schiff Base

Test Sample (mg/mL)	**Zone of Inhibition (mm)**
8	12.2 ± 0.4
4	9.7 ± 0.6
2	7.5 ± 0.5
1	5.3 ± 0.3
0.5	3.0 ± 0.2
Gentamicin (10 µg)	22.5 ± 0.5
DMSO (1%)	0.0

The highest concentration (8 mg/mL) produced a **zone of inhibition of ~12.2 mm**, confirming significant bacteriostatic potential. While the reference antibiotic gentamicin displayed superior inhibition (~22.5 mm), the Schiff base showed **comparable activity relative to structurally similar hydrazone derivatives** reported in the literature, which often exhibit moderate to strong inhibition against Gram-negative pathogens including *Klebsiella* species.

Conclusion

In this study, A novel hydrazone Schiff base, (2E)-1-cyclohexyl(phenyl)methylene-2-4-chlorobenzylidene) hydrazine was synthesized by using simple condensation method. The formation of the target molecule was spectroscopically characterized based on FT-IR and the use of the ^{1}H NMR technique to identify the two azomethine (C=N) bonds and distinctive aromatic and aliphatic proton peaks. The use of conjugated aromatic systems, cyclohexyl group and the chloro substituent led to a structurally stable lipophilic molecule. The product of the synthesis showed moderate to good antibacterial activity with Klebsiella pneumoniae with a concentration-dependent zone of inhibition and a zone of 2.0 mg/mL of MIC. The activity was lower than with the standard antibiotic gentamicin though the results are comparable to those of structurally related hydrazones Schiff bases. The antibacterial activity is probably connected with the existence of the azomethine group, which disrupts bacterial enzymatic processes, and the enhanced lipophilicity that allows the penetratory effect on the bacterial cell membrane. These finding shows that the hydrazone Schiff bases with halogenated aromatic rings can be used as promising antibacterial drugs. It is suggested that further research, such as those on structure-activity relationships, as well as testing them against a wider microbial strain population, should be done to improve their therapeutic potential in future.

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