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# Synthesis of Macrocyclic Schiff Bases Derived from 1,4-Dihydrapyridine and Their Anti-Cancer Cytotoxic Effect and Anti-bacterial activity

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## Abstract

This study involves the preparation of macrocyclic Schiff bases (R4-R8) through two steps, first step involves the preparation of macroacyclic Schiff bases (R1-R3) by the reaction of 3,5-diacety l-2,6-dimethyl-1,4-dihyropyridine DHP(R) with diamine derivatives (4-methyl 1,2-phenelene diamine, 1,4-phenelene diamine and hydrazine hydrate). The second step involves the synthesis of macrocyclic Schiff bases (R4-R8) via cyclization of acyclic schiff bases (R1-R3) which are further reacted with diketone derivatives (benzil, acetyl acetone and 3,5-diacetyl-2,6-dimethy l-1,4-dihyropyridine). The condensation reactions were carried out using both conventional reflux and microwave-assisted methods to evaluate the efficiency and yield of each approach. The synthesized compounds were analyzed and identified through proton nuclear magnetic resonance ($^{1}$H NMR) spectroscopy and fourier-transform infrared (FT-IR) spectroscopy and nuclear magnetic resonance ($^{13}$C NMR), indicating that the Schiff bases structures had been successfully formed, conforming the bonding arrangement and offering insight into the structural characteristics of the macrocyclic system. The cytotoxic effect of one of the synthesized compounds (R5) was assessed against MCF-7 breast cancer cell line using the MTT assay technique, whereas (R1, R2 and R5) were examined for their antibacterial activity using the agar well diffusion assay.

**Keywords:** Schiff Base, Macrocyclic Compounds, Anticancer, Microwave, DHP.

## Introduction

Macrocyclic compounds are molecules containing large ring structures, minimum 9 or more atoms, they often include heteroatoms (like N, O, S and maybe p) [1].

The broad interest in macrocycles in various scientific domains began to grow a few years prior to 1980 and then sharply surged starting in 1990 and onward, it sharply increased [2]. Natural products were the source of the first known macrocyclic chemicals. Porphyrins, which are present in hemoglobin and chlorophyll before structural studies in the early 20th century. Macrocycles that are most extensively researched are Schiff base macrocycles and their complexes [3]. Macrocyclic compounds exhibit interesting properties such as high binding selectivity, stereochemical rigidity, and biological activity [4][5]. Because of their numerous uses in supramolecular chemistry and biology as well as their abundance in nature, those kinds of molecules have grown in significance [6], cancer therapeutic agents [7], antimicrobial, antibacterial, antifungal, antioxidant , anti-inflammatory, and antidiabetic [8] [9][10][11] and [12]. They are also used as luminescence chemosensors [13], Metal-coordinated macrocyclic compounds have been successfully used as catalysts in a number of significant organic reactions [14].

**Experimental:**

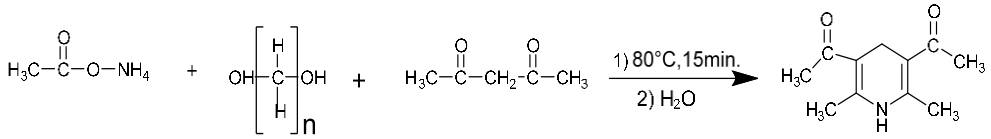
**Chemicals and Instrumentations:**

The chemicals utilized in this research were obtained from the Fluka, BDH, Aldrich. Melting points (°C) were measured using a Stuart SPM30 apparatus in open glass capillaries which was uncorrected, the measurements were conducted at the Department of Chemistry, College of Science, University of Mosul. Infrared (IR) spectra were recorded using a Bruker spectrometer in the range 400 to 4000 $cm^{-1}$ at the same department.$^{1}$H-NMR and $^{13}$C-NMR spectra were recorded on a Bruker 400 MHz spectrometer at Al-Basrah University, Iraq, employing tetramethylsilane (TMS) as the internal standard and DMSO as the solvent. The anticancer evaluation of compound R5 was carried out at CAC Laboratory Testing Center (Baghdad-Iraq). The antibacterial evaluation of compound R1, R2 and R5 carried out at the Department of Biology, College of Science, University of Mosul.

**Synthesis 3,5- Diacetyl-2,6-Dimethyl-1,4- Dihyropyridine DHP(R):** [15][16]

A mixture of paraformaldehyde (4.8 g, 0.16 mole), acetylacetone (32 g, 0.32 mole), and ammonium acetate (18.5 g, 0.24 mole) was introduced into a 250 mL

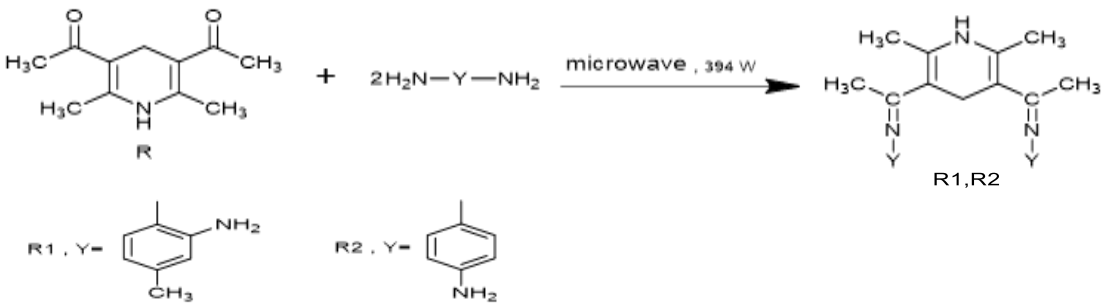
round-bottom flask. The reaction was carried out under stirring at 80 °C for approximately 15 minutes, following the conventional Hantzsch reaction. The reaction mixture was allowed to cool to ambient temperature, water was then added gradually with continuous stirring by glass rode, resulting in the formation of a yellow precipitate. The solid was isolated by filtration, thoroughly washed with cold water, and air-dried. The crude product was purified by recrystallization from methanol and subsequently dried, yellow powder was obtained in 57.7% yield. The melting point of the final compound was recorded at 215–217 °C, closely matching the literature value of 213–215 °C.




Equation1: Synthesis of starting material (R)

**Synthesis of Macroacyclic Schiff Bases (R1-R2):**

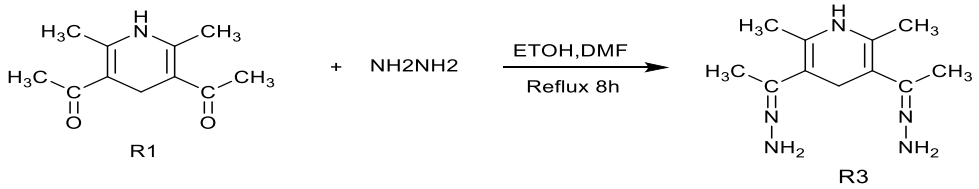
(0.0026 mole, 0.5g) of 1,4-dihydropyridine (DHP) was reacted with (0.0052 mole) of a diamine derivatives (4-methyl 1,2-phenelene diamine, 1,4-phenelene diamine). The reactants were first thoroughly ground together using a mortar and pestle to ensure intimate mixing and uniformity. The resulting mixture was then transferred into a beaker and subjected to microwave irradiation at 394 watts for (6-12 min.). The reaction mixtures allowed to reach room temperature on its own. Petroleum ether was used to wash each raw material. The solid products were subsequently precipitated using diethyl ether, isolated by filtration, and dried to obtain the final compounds (R1, R2) as shown in equation2.




Equation 2: preparation macroacyclic Schiff bases (R1-R2)

**Synthesis Compound Macroacyclic Schiff Base R3:**

A solution was by dissolving 1.5 g (0.01 mole) of 1,4-dihydropyridine (DHP) in 20 mL of absolute ethanol followed by the addition of 5 mL of DMF to aid solubility. Then 1.0 g (0.02 mole) of 98% hydrazine hydrate was added gradually with continuous stirring. The resulting reaction mixture was subsequently heated under refluxed at 80 °C for 8 hours. The reaction progress was regularly monitored using thin-layer chromatography (TLC) using ethyl acetate: benzene in a (4:6) ratio. Upon completion, the mixture was left at room temperature overnight to promote crystallization. The precipitate was collected by vacuum filtration, and subsequently washed with cold ethanol to eliminate remaining impurities, and dried. A white crystalline solid was obtained in 52% yield, with a melting point of 286–289 °C (R3) as illustrated in equation3. Table 1 show some physical properties of prepared compounds (R1-R3).



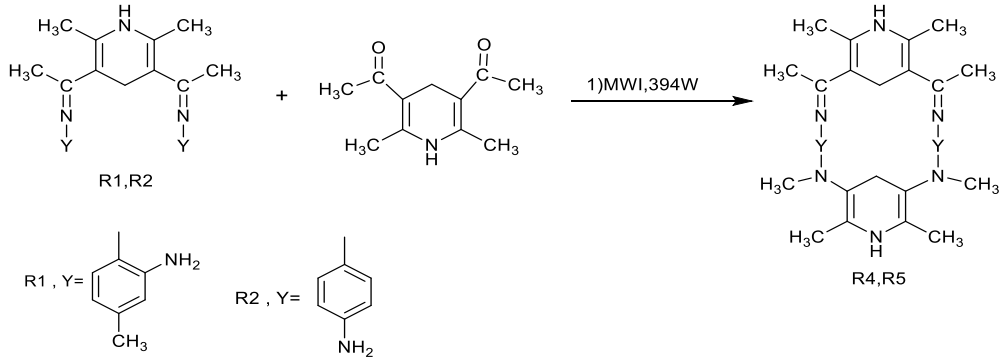

Equation 3: preparation Schiff bases (R3)

**Synthesis of Macrocyclic Compounds (R4-R5):**

Macrocyclic compounds were synthesized through the cyclo condensation of macroacyclic Schiff bases (R1, R2) with 1,4-dihydropyridine (DHP) derivatives (R) under microwave irradiation. (0.0013 mole) macroacyclic Schiff bases and (0.0013, 0.2g) of DHP were thoroughly mixed by grinding in a mortar to ensure homogeneous

Distribution of the starting materials. The resulting solid mixture was then transferred to a microwave-compatible reaction vessel (beaker) and irradiated to microwave irradiation at (394) watts for a duration of (8min.). Completion of the reaction was monitored by a visible color change and confirmed by thin-layer chromatography (TLC) using (ethyl acetate: benzene) in a ratio (4:6). The reaction mixtures were left to cool naturally to room temperature. The crude products were washed with petroleum ether. Macrocyclic products were subsequently

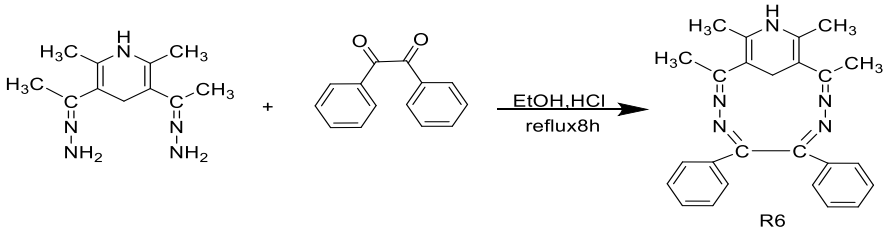
precipitated and recrystallized by the addition of diethyl ether, isolated by vacuum filtration, and dried under reduced pressure to afford the final macrocyclic compounds (R4-R5) as shown in equation 4.



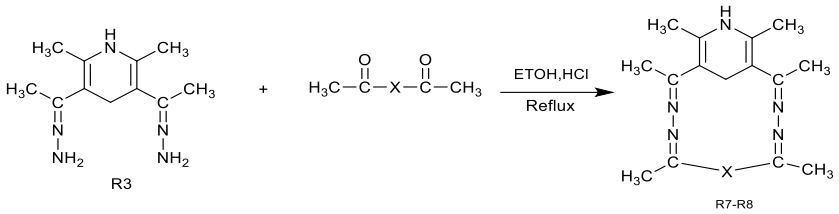

Equation 4: preparation of macrocyclic Schiff bases (R4, R5)

**Synthesis of Macrocyclic Schiff Bases (R6-R8):** [17]

Macrocyclic Schiff bases (R6-R8) were synthesized through the condensation of the hydrazone (R3) with various di ketones, including (benzil, acetylacetone, and 3,5- diacetyl-2,6-dimethyl -1,4-dihydropyridine). In a typical procedure, (0.0009 mole, 0.2g) of (R3) was dissolved in hot ethanol, and (0.0009mole) of the selected diketone was also dissolved separately in hot ethanol. The hydrazone was then added dropwise to the diketone solution, under constant stirring and the pH was adjusted to approximately 3 by adding concentrated hydrochloric acid dropwise, the prepared solution was refluxed at 80 °C for 10hours. The reaction was deemed complete based on TLC analysis using (ethyl acetate: benzene) in a (4:6) ratio. The solvent was then evaporated under vacuum, and the concentrated mixture was then placed in an ice bath to initiate crystallization. The formed solid was filtered off, and washed by using cold ethanol, then dried (R6-R8) formed as shown in equations $5_a$ and $5_b$. Table 1 show some physical properties of (R1-R8).




Equation 5a: preparation of macrocyclic Schiff base (R6)




Equation 5b: preparation of macrocyclic Schiff bases (R7, R8)

Table (1): physical properties of prepared compounds (R1-R8)

| Compounds No. | Name of compounds | Melting point | Yield % | Color |
|---|---|---|---|---|
| R1 | 6,6'-(((2,6-dimethyl-1,4-dihydropyridine-3,5-diyl)bis(ethan-1-yl-1-ylidene))bis(azaneylylidene))bis(3-methylaniline) | 125-127 | 63.4 | Yellow-greenish |
| R2 | 4,4'-(((2,6-dimethyl-1,4-dihydropyridine-3,5-diyl)bis(ethan-1-yl-1-ylidene))bis(azaneylylidene))dianiline | 131-134 | 88 | Yellow-greenish |
| R3 | 3,5-bis(1-hydrazineylideneethyl)-2,6-dimethyl-1,4-dihydropyridine | 287-289 | 72 | white |
| R4 | 6,8,13,17-(2',6'-dimethyl-1',4'-dihydropyridine)-2,3,11,12-(3'-methylbenzene)-5,9,14,18-tetramethyl-1,4,10,13-tetraazacyclooctadecane | 194-197 | 73 | Deep brown |
| R5 | 8,1019,21-(2',6'-dimethyl-1',4'-dihydropyridine)-2,5,13,16-dibenzene-7,11,18,22-tetramethyl-1,6,12,17-tetraazacyclodocosane | 189-193 | 68 | brown |
| R6 | 4,6-(2`,6`-dimethyl-1`,4`-dihydropyridine)-10,11-diphenyl-3,7-dimethyl-1,2,8,9-tetraazacycloundecane | >300 | 58 | White |
| R7 | 4,6,11,13-(2`,6`-dimethyl-1`,4`-dihydropyridine)-3,7-dicarbonyl-10,14-dimethyl-1,2,8,9tetraazacyclotetradecane | 299-301 | 60 | White |
| R8 | 4,6-(2`,6`-dimethyl-1`,4`-dihydropyridine)-3,7,10,12-tetramethyl-1,2,8,9-tetraazacyclododecane | >300 | 62.5 | White |

## Results and disscution

The research was conducted in three steps, first step include synthesis the starting material, 3,5-diacetyl-2,6-dimethy l-1,4 -dihydropyridine DHP(R),via Hantzsch reaction. This multicomponent reaction involved paraformaldehyde, acetylacetone, and ammonium acetate as starting reagents. In the second step, the synthesized DHP was reacted with various diamine derivatives, employing two different synthetic methods: microwave technique synthesis and conventional reflux method. These reactions lead to the formation new macroacyclic Schiff base derivatives (R1-R3). The third step involved the cyclization of acyclic derivatives (R1-R2) with DHP via microwave irradiation leading to the formation of macrocyclic Schiff bases (R4-R5). In contrast, compound R3 was refluxed with

diketone derivatives in the presence of concentrated HCl (R6-R8). It's worth mentioning that some of these reactions have been traced by TLC chromatography by using (ethyl acetate: benzene) in a (4:6) ratio. The structures of prepared compounds have been characterized by their FT-IR, $^{1}$HNMR and $^{13}$CNMR analysis.

The starting material DHP was characterized by FT-IR spectrum and it is melting point which were agreement with published data [15]. The main features of the FT-IR spectra of DHP as shown in figure1 are presence of three bands, band(I) strong absorption band at 3381cm$^{-1}$ indicating the existence of NH group, band (II) observed at 1671cm$^{-1}$ refers to C=O stretching vibration. Band (III) at 1643cm$^{-1}$ is due to C=Cpyridine stretching vibration.

The FT-IR spectra for acyclic Schiff bases (R1-R3) showed the major absorption bands at (3078-3374) cm$^{-1}$ for NH and $NH_2$ groups, (1589-1677)cm$^{-1}$ return to C=N stretching vibration which indicates the formation of these compounds. Other absorption bands were represented in the table 2, figures 2 and 3 show the FT-IR spectra for (R1, R3).

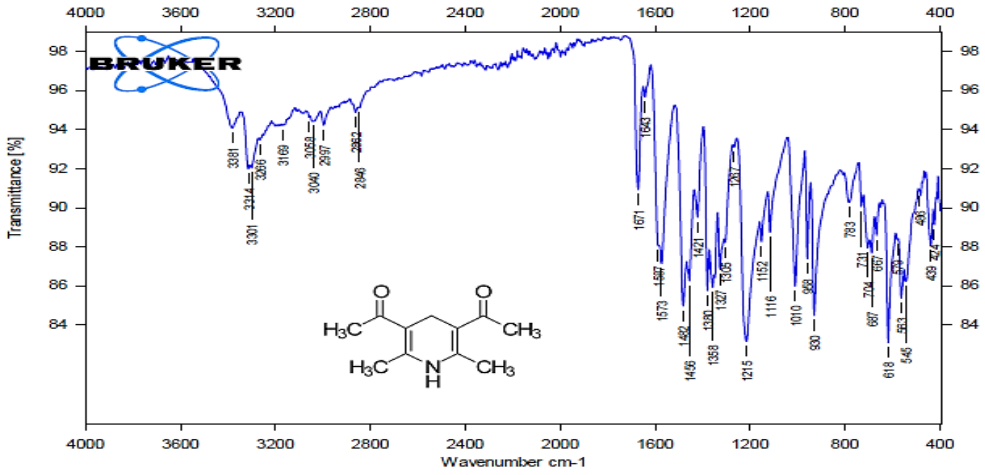



Figure (1): FT-IR of compound R

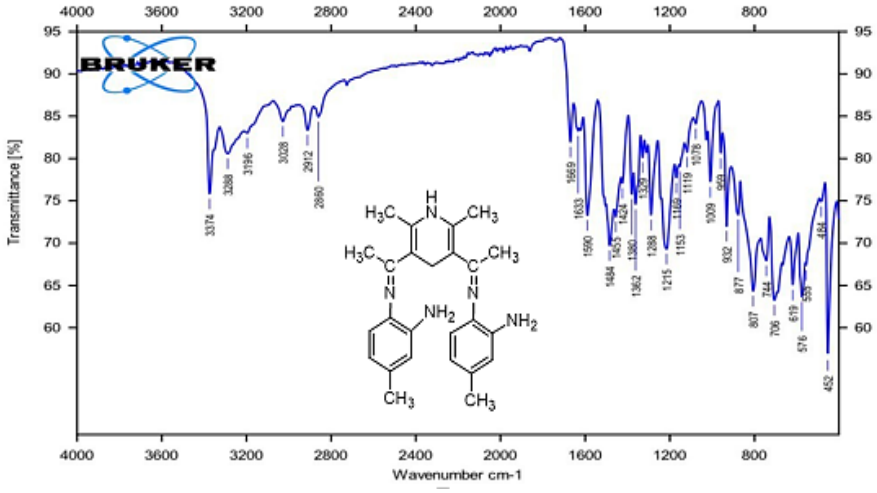



Figure (2): FT-IR of compound R1

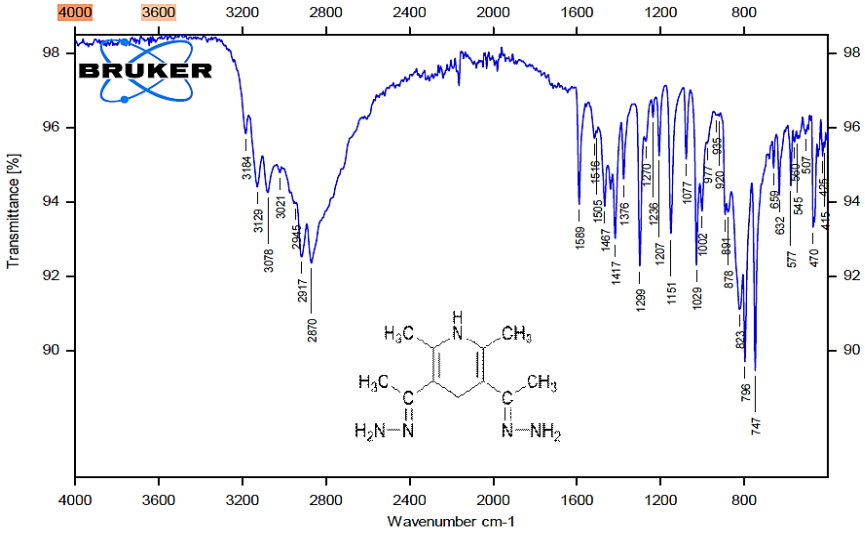



Figure (3): FT-IR of compound R3

The [1]HNMR spectra of the compounds (R2-R3) were in agreement with the suggested structures. In compound R2 (figure 4), the proton of NH pyridine gives at 8.326 ppm equivalent to one proton, aromatic proton appeared at 6.36 ppm as singlet band equivalent to eight protons, other important signal appeared as abroad band at 4.184ppm belong to two groups of NH2. Honesty, the integration for the aromatic protons band gave a higher number of protons than expected which gives an indication that the compound is impure. The compound R3 had signals at

11.878 ppm refers to NH group equivalent to one proton, band at 4.447ppm belong to two groups of $NH_2$. Other proton chemical shifts are presented in table (3). The $^{13}$CNMR spectra in compound R2 shown the most important signal at 159.17ppm belong to C=N. In compound R3, the band which belong to C=N appear at 146.21[18], figure 5 illustrated the $^{13}$CNMR of compound R2, other carbon chemical shifts are presented in table (3).

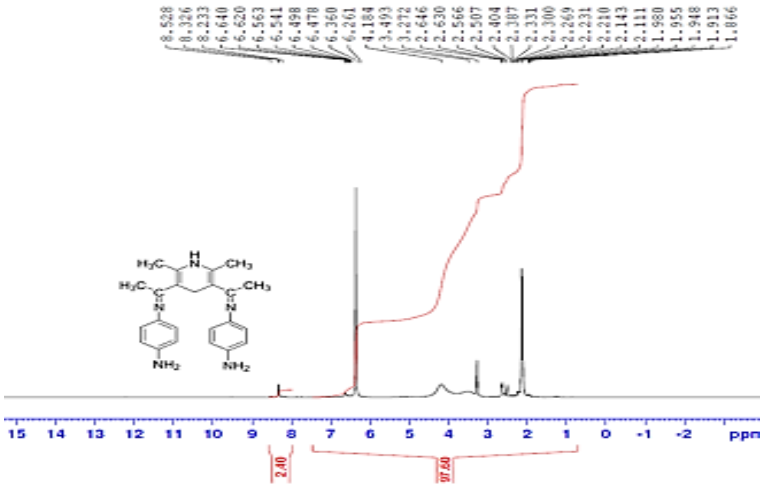


Figure (4): $^{1}$H-NMR spectrum of compound R2

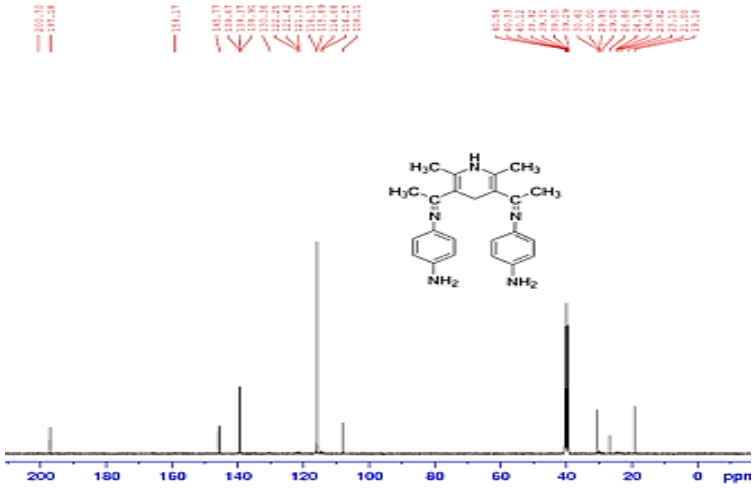


Figure (5): $^{13}$CNMR of compound R2

The cyclization of acyclic Schiff bases (R1-R3) with the various carbonyl compounds resulted in the formation of macrocyclic schiff bases (R4-R8). The general absorption bands observed in the FT-IR spectra of these products

illustrated in table (2). The spectra showed the absence of amino group frequency in the region (3129-3343) $cm^{-1}$ in the starting materials (R2-R3) which gives a good indication about the formation of these compounds. In compounds (R7, R8), the absorption NH bands appears at (3141, 3120) $cm^{-1}$ respectively, (3090&3049) $cm^{-1}$ belong to overtone of NH bending. The absorption band C=N appears at (1587, 1678) $cm^{-1}$respectivly [19], figure 6 show the FT-IR of compound R7.

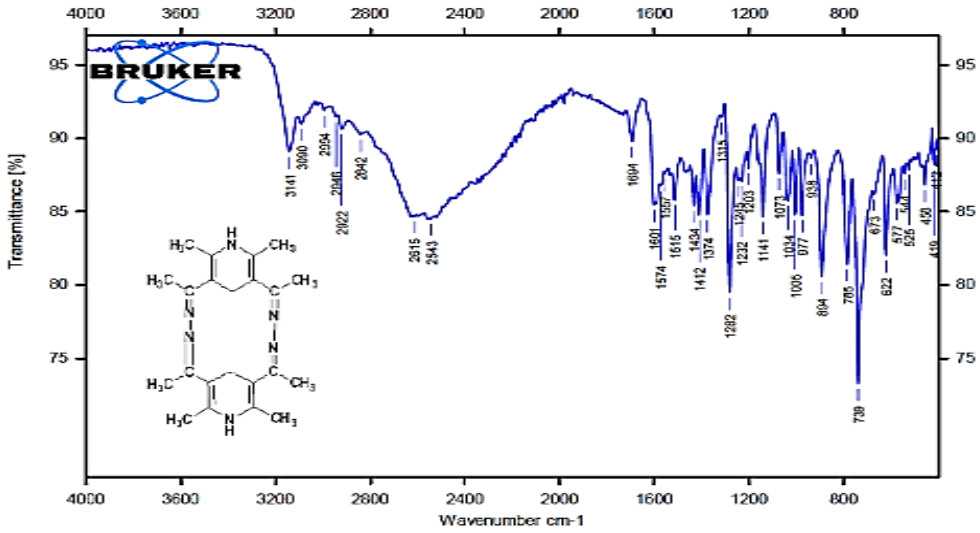



Figure (6): FT-IR of compound R7

$^{1}$HNMR spectra also gives the extra information about the absence of amino group signals at (4.422&4.184) ppm in compounds (R2, R3). The $^{1}$HNMR for the compound (R5, R7) gave signals at (8.315, 8.570) ppm as a singlet band belong to 2NH groups, (3.260, 3.501) ppm equivalent four protons belong to $2CH_2$pyridine groups. These compounds also shows another singlet band at (2.257, 2.116) ppm belong to $CH_3$pyridine groups. Finally CH3imine groups gives a singlet band at (2.224 & 2.650) ppm figure 7 and 8 show the $^{1}$HNMR of compound (R5, R7). The $^{13}$CNMR spectra gives the most important signals at (158.93, 159.17) ppm which belong to imine group. Other carbon chemical shift are presented in Table (3). Figure 9 and 10 show the $^{13}$CNMR of (R5, R7).

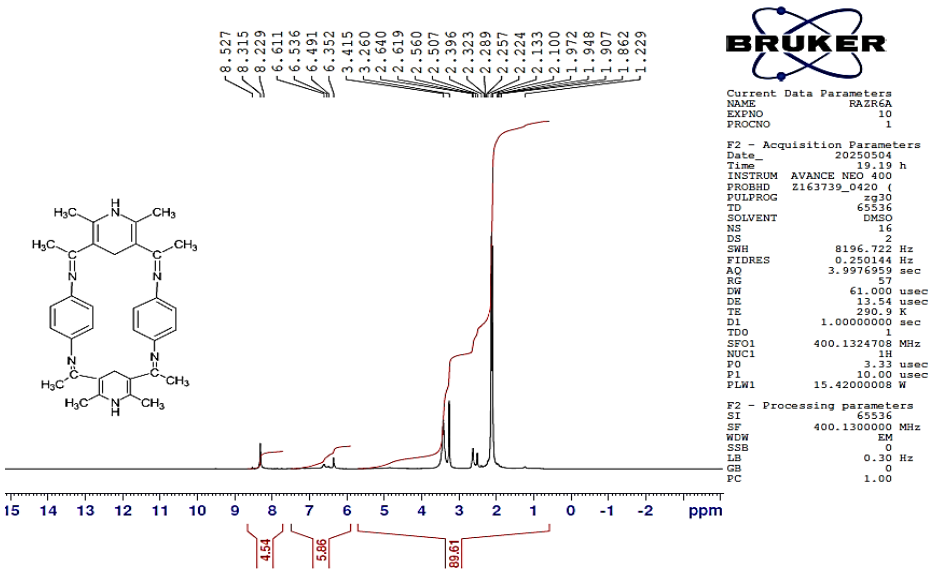



Figure (7): [1]H-NMR spectrum of compound R5

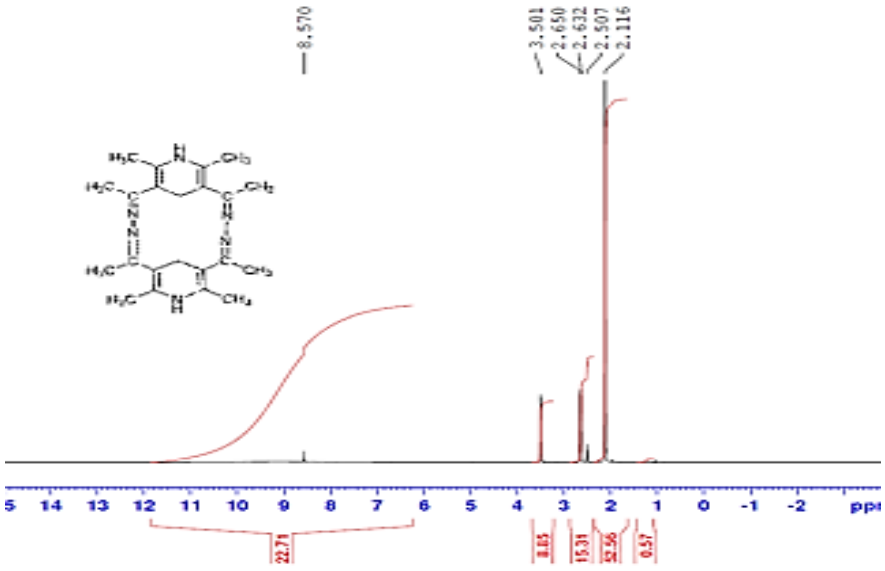



Figure (8): [1]H-NMR spectrum of compound R7

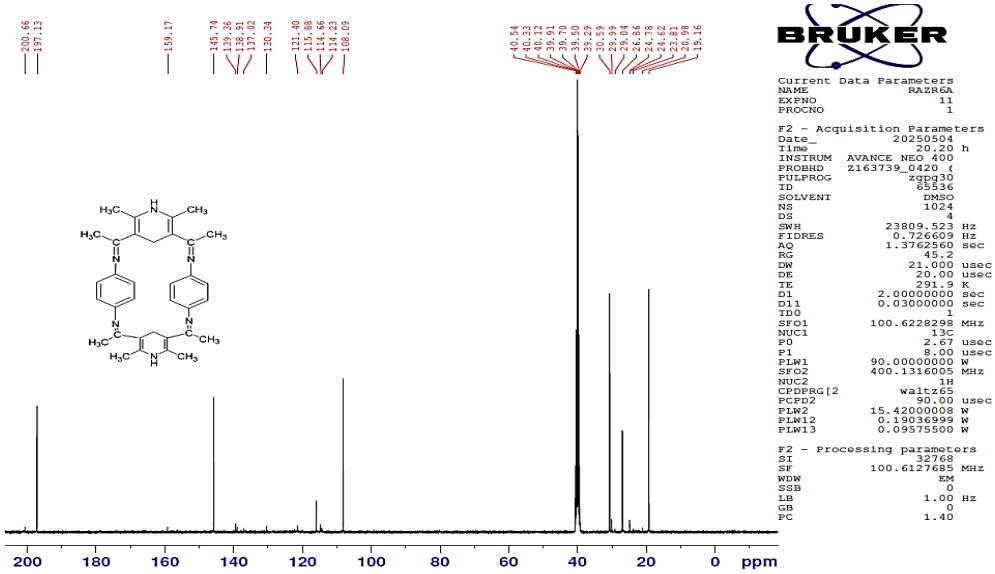



Figure (9): $^{13}$C-NMR spectrum of compound R5

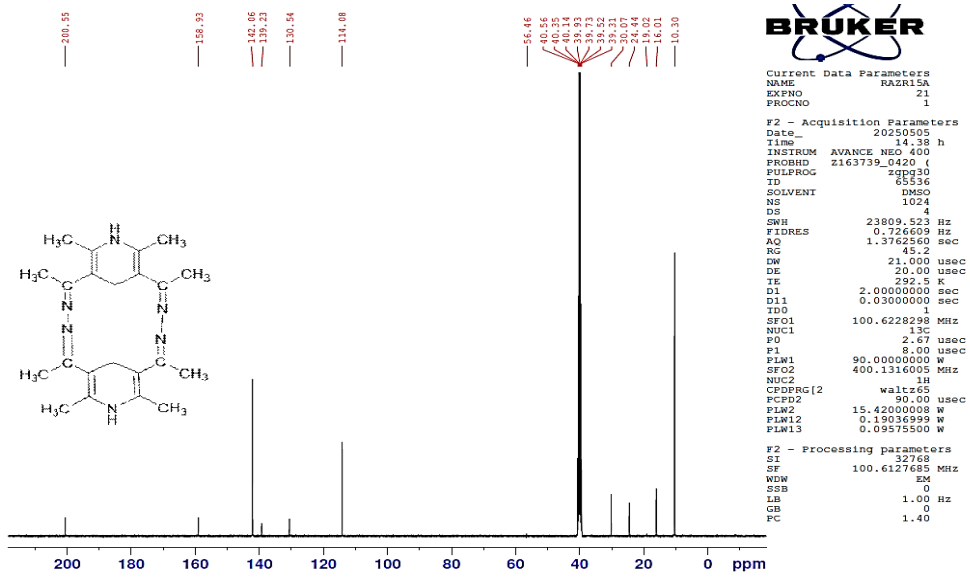



Figure (10): $^{13}$C-NMR spectrum of compound R7

Table (2): FT-IR bands of the prepared compounds (R1-R8)

| No. of compounds | C=N | NH | NH2 | C=C pyridine | C-C aromatic | C-H aliphatic | C-H aromatic |
|---|---|---|---|---|---|---|---|
| R1 | 1669 | 3191 | 3288-3374 | 1633 | 1590 | 2912-2860 | 3028 |
| R2 | 1677 | 3221 | 3299-3343 | 1630 | 1571 | 2992-2862 | 3052 |
| R3 | 1589 | 3078 | 3129-3184 | 1516 | _ | 2917-2870 | _ |
| R4 | 1678 | 3315 | _ | 1629 | 1572 | 2993 | 3052 |
| R5 | 1677 | 3299 | _ | 1657 | 1574 | 2924-2862 | 3006 |
| R6 | 1587 | 3120 | _ | 1519 | 1469 | 2922 | 3049 |
| R7 | 1640 | 3114 | _ | 1601 | _ | 2946-2922 | _ |
| R8 | 1587 | 3049 | _ | 1520 | _ | 2924 | _ |

Table (3): $^{1}$H-NMR and $^{13}$C-NMR of prepared compounds (R2, R3, R5 and R7):

| No. of compound | $^{1}$H-NMR (ppm) | $^{13}$C-NMR(ppm) |
|---|---|---|
| R2 | 8.528($NH_{pyridine}$,S,1H),6.360($H_{arom}$, S,12H), 4.184($4NH_2$,S,8H), 3.272($CH2_{pyridine}$) ,2.210&2.111 (4CH3,ss,12H) | C=N(159.17),C-$C_{arom.}$(145.77,138.91,122.25-121.33,116.17),C=$C_{pyridine}$(139.67,139.37,108.11,30.61) ,$CH3_{imine}$(26.82), $CH3_{pyridine}$(19.18) |
| R3 | 11.87($NH_{pyridine}$,S,1H),4.44-4.422($NH_2$,weak) ,3.313 ($CH_{2pyridine}$,S,2H),1.970($4CH_3$,S,12H) | C=N (146.21), C=$C_{pyridine}$ =(113.21,56.49), $CH3_{imine}$ (19.03), $CH3_{pyridine}$ (17.14) |
| R5 | 8.315($NH_{pyridine}$ , S, 2H ), 6.352-6.611($CH_{arom}$. m.), 3.260($2CH2_{pyridine}$,s,4H), 2.257($CH3_{pyridine}$,s,12H),2.224($CH3_{imine}$,s, 12H) | C=N(159.17),$CC_{arom.}$=(145.74,130.34,121.40,115.88), ,C=$C_{pyridine}$(139.36,108.09), $CH2_{pyridine}$ =(30.59), $CH3_{imine}$ =(29.8604,24.78), $CH3_{pyridine}$=(20.98,19.16) |
| R7 | 8.570($NH_{pyridine}$,s,2H), 3.501($CH2_{pyridine}$,s,4H), 2.650($CH3_{imine}$,s,12H),2.116($CH3_{pyridine}$,s, 12H) | C=N (158), C=$C_{pyridine}$ =(142.06, 139.23,130.54), $CH3_{imine}$=(24.44,19.02), $CH3_{pyridine}$ =(16.02,10.30) |

## Cytotoxicity Assay: [20]

Compound R5 was determined to cytotoxic evaluation against human breast cancer cell line (MCF-7) using MTT assay. The test involved seeding MCF-7 cells at a density of 7000 cells/well in 96-well plates, followed by a 24-hour incubation period at 37 C in a highly humidified environment with 5% CO2. The medium was removed after incubation, and 100 µL of compound-containing media containing the designated concentrations was added. Under identical conditions, the plates were incubated for an additional 72 hours. After the patient received treatment for 72 hours, the culture material was removed. The MTT solution (0.5

mg/mL in phosphate buffered saline solution, or PBS) was added to each well in a volume of 20%. Once more, plates were incubated at 37°C for 3–4 hours. After removing the MTT solution, 100 µL of DMSO was added to each well to dissolve the formazan crystals. The absorbance at 570 nm was measured using an ELISA reader. The test was conducted four times with varying concentrations of the chemical, and the average readings were obtained. The solvent employed was DMSO [21].The MCF-7 cancer cell line was used to test compound R5's anti-proliferation activity, and it was discovered that the MTT's yellow hue changed to a formazan purple hue. Compound R5 showed the following inhibition (viability %) 100, 93, 91, 91, 90, 90, 84, 25, 11at doses of (0, 1.17, 2.34, 4.68, 9.37, 18.75, 37.5, 75, and 150) µg/ml, respectively (Table4, Figure 11). Also, compound R5 did show the LC50 value (a measure of the concentration of a compound that is lethal to 50% of cancer cells) equal to **79.6 µg/ml**. This is indicate that the selective compound R5 has a strong cytotoxic activity[22].

Table (4): The effect of compound R5 on the MCF-7 cancer cell at $37^0$C for 72 hours

| **Concentration (µg/ml)** | **0** | **1.17** | **2.34** | **4.68** | **9.37** | **18.75** | **37.5** | **75** | **150** |
|---|---|---|---|---|---|---|---|---|---|
| Dilution Ratio | 0 | 1:128 | 1:64 | 1:32 | 1:16 | 1:8 | 1:4 | 1:2 | 1:1 |
| Test1 | 0.576 | 0.496 | 0.522 | 0.515 | 0.509 | 0.49 | 0.45 | 0.135 | 0.061 |
| Test2 | 0.583 | 0.524 | 0.511 | 0.497 | 0.51 | 0.506 | 0.506 | 0.145 | 0.054 |
| Test3 | 0.53 | 0.523 | 0.507 | 0.523 | 0.507 | 0.519 | 0.463 | 0.142 | 0.055 |
| Test4 | 0.563 | 0.55 | 0.513 | 0.51 | 0.509 | 0.505 | 0.473 | 0.147 | 0.087 |
| Mean | 0.563 | 0.523 | 0.513 | 0.511 | 0.509 | 0.505 | 0.473 | 0.142 | 0.064 |
| Viability | 100 | 93 | 91 | 91 | 90 | 90 | 84 | 25 | 11 |
| Standard variation (SD) | 0.024 | 0.022 | 0.006 | 0.011 | 0.001 | 0.012 | 0.024 | 0.005 | 0.015 |

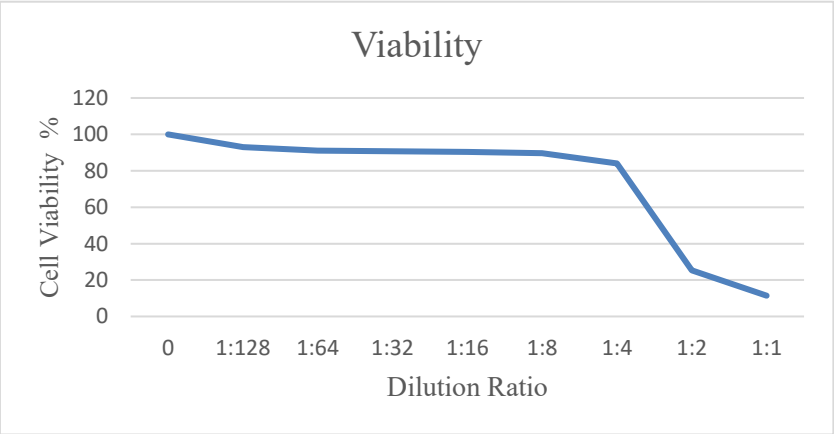



Figure (11): The effect of compound R5 on MCF-7 cell line by MTT assay

**Antibacterial Activity:**

The antibacterial potential of compounds (R1, R2, and R5) was assessed against the Gram-positive bacterium ***Exiguobacterium indicum*** using the agar well diffusion assay. The inoculated plates were incubated at 37 °C for 24 h, and Measurements were carried out on the day after, with the samples dissolved in DMSO at a concentration of 1 µg/ml. Figure 12 shown that compound R1, R2 and R5, exhibited no antibacterial activity against the mentioned bacterial, likely maybe due to the low concentration of the samples for which the biological activity was measured... (1=R5,2=R2,3=R1).

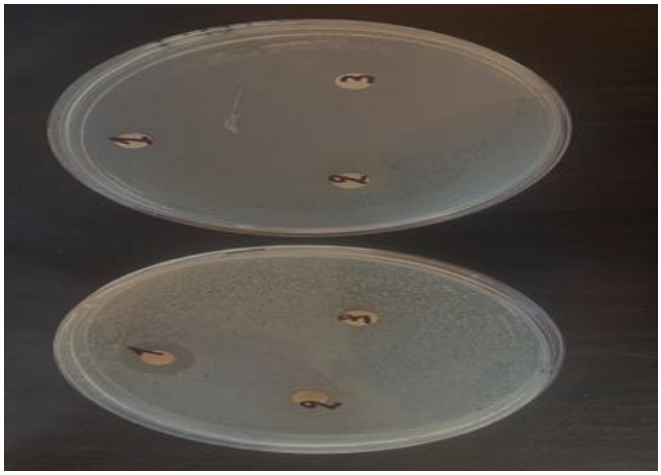


Figure (12): The antibacterial activity of compounds (R1, R2 andR5)

## Conclusion

In this study, both macrocyclic and macroacyclic Schiff bases were successfully synthesized using 2,6-dimethyl-1,4-dihydropyridine as the starting material. The synthesis was carried out through a multi-step process employing both conventional and green methodologies. Initially, macroacyclic Schiff bases were prepared, which were subsequently cyclized through reactions with various diketones to yield the corresponding macrocyclic Schiff bases. The synthesized compounds were thoroughly characterized using a range of spectroscopic techniques, including FT-IR, $^{1}H$ NMR, and $^{13}C$ NMR. These analyses confirmed the chemical structures and provided valuable information about their properties. Additionally, physical characteristics such as melting points, colors, and yields

were recorded, supporting the successful formation of the target compounds. The compound R5 was tested for cytotoxicity activity on MTT assay method and the results showing that the compound has a strong cytotoxicity activity towards MCF7 cell lines. In contrast Compounds R1, R2, and R5 were tested for antibacterial activity; which they are inactive.

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