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Synthesis and Antibacterial Screening of New Schiff Bases Based on N-(4-acetophenyl) Succinimide

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Abstract

A series of nine new Schiff bases based on N-(4-acetophenyl)succinimide were synthesized via multistep synthesis. In the first step N-(4-acetophenyl)succinamic acid was prepared via reaction of succinic anhydride with 4-aminoacetophenone. The prepared amic acid was dehydrated in the second step producing N-(4-acetophenyl)succinimide. The prepared succinimide represents a modified methyl ketone bearing succinimde cycle and ready for introducing in condensation reaction thus in the third step the prepared imide was introduced in acid-catalyzed condensation reaction with a variety of primary aromatic amines affording the new target Schiff bases. The results of antibacterial screening of the newly synthesized Schiff bases indicated that they possess high antibacterial activity.

Keywords: N-(4-acetophenyl)succinimide, schiff bases, Succinamic acids

تحضير وتقييم الفعالية المضادة للبكتريا لقواعد شيف جديدة اعتماداً على N –(4– اسيتوفنيل) سكسن ايمايد

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الخلاصة

تضمن البحث تحضير تسعة قواعد شيف جديدة اعتماداً على N–(4–اسيتوفنيل) سكسن ايمايد بتطبيق التحضير متعدد الخطوات. تم في الخطوة الاولى تحضير المركب N–(4– اسيتوفنيل) حامض السكسن آميك وذلك من خلال تفاعل حامض السكسنيك اللامائي مع 4–امينو اسيتوفينون اما في الخطوة الثانية فقد تم سحب الماء من حامض الآميك المحضر وبذلك تم تحويله الى N–(4–اسيتوفنيل) سكسن ايمايد. يمثل الايمايد المحضر مثيل كيتون مرتبطاً بحلقة سكسن ايمايد يمكن ادخاله في تفاعل التكاثف في الخطوة الثالثة والتي تضمنت ادخال الايمايد في تكاثف مع امينات اولية اروماتية مختلفة مما اسفر عن تكوين قواعد شيف الجديدة المطلوبة. اظهرت نتائج دراسة الفعالية المضادة للبكتريا لقواعد شيف المحضرة بانها تمتلك فعالية عالية مضادة للبكتريا.

Introduction

Schiff bases the condensation products of carbonyl compounds and primary amines are an important class of organic compounds that belong to widely used group of organic intermediates [1,2] used for production of different pharmaceuticals [3,4] and potent molecules [5]. Moreover, Schiff bases are also known to possess different biological activities like anticancer [5], antibacterial [6, 7]

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and herbicidal activities. Schiff bases also have many uses as dyes, polymer additives, corrosion inhibtors and as ligands for complexation with metal ions [8-10]. On the other hand cyclic imides are a valuable group of bioactive compounds that show antimicrobial, antitumor, antiviral and anti-inflammatory properties [11-13]. Besides they are important building blocks for synthesis of drugs, advanced materials, polymers and natural products [14-16].

Keeping all these points in mind it seems worthwhile to combine these two active segments (Schiff base and cyclic imide) simultaneously in the same molecule followed by investigation its biological activity. Thus the present work involved synthesis of new Schiff bases bearing succinimide cycle based on N-(4-acetophenyl)succinimide which introduced in condensation with different primary aromatic amines.

Experimental

All the used chemicals and solvents were of reagent grade. Uncorrected melting points were recorded on GallenKamp melting point apparatus. FTIR spectra were recorded on Shimadzu-FTIR 8400 Fourier Transform Infrared Spectrophotometer. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on near magnetic resonance Bruker, Ultrasheild 300 MHz using tetrametyl silane as internal standard and DMSO-d6 as a solvent.

1- Preparation of N-(4-acetophenyl)succinamic acid (1)

The titled compound was prepared according to literature procedures [11, 12] via reaction of equimolar amounts of succinic anhydride and 4-aminoacetophenone. The resulted solid was purified by recrystallization from ethanol and afforded as ayellow crystals in 84% yiled with melting point =203-205°C.

2- Preparation of N-(4-acetoxy phenyl)succinimide (2)

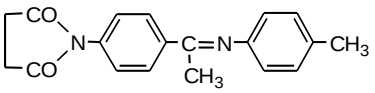
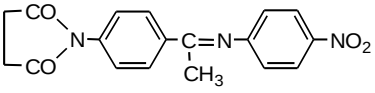
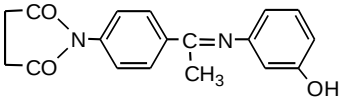
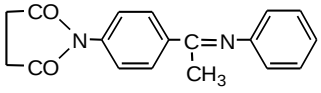
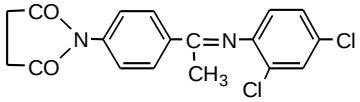
Compound (2) was prepared according to literatures [11, 12] via treatment of compound (1) (0.01 mol, 2.35 g) with acetic anhydride (25 mL) and anhydrous sodium acetate (0.125 g) under reflux followed by pouring in excess cold water. The resulted solid was recrystallized from cyclohexane producing white crystals in 72% yield with melting point = 162-163°C.

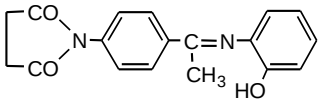
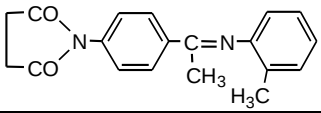
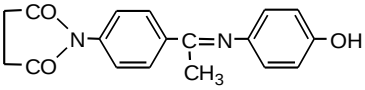
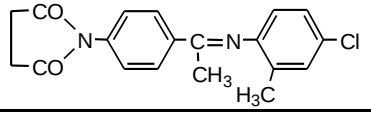
3- Preparation of Schiff's bases 4-(N-succinimidyl)phenyl methyl substituted benzylidene (3-11)

A mixture of compound (2) (0.01 mol, 2.17 g) and primary amine (0.01 mol) dissolved in (20 mL) of absolute ethanol in the presence of few drops of glacial acetic acid was refluxed for six hours [17].

The resulted solid was filtered, dried then recrystallized from a suitable solvent. Physical properties of Schiff bases (3-11) are shown in Table-1.

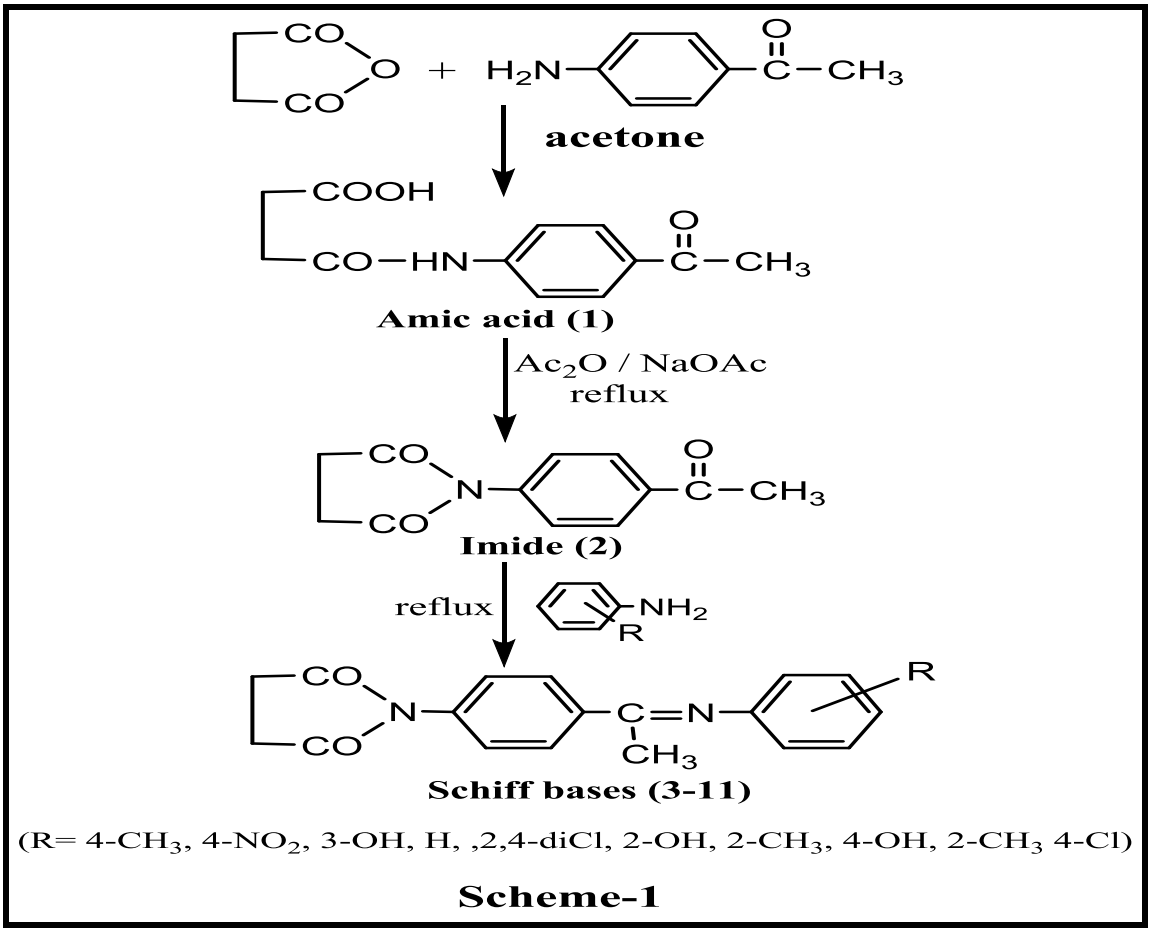
Table 1- Physical properties of Schiff bases (3-11)

Comp. No.	Compound structure	Colour	Melting point °C	Yield%	Recrystallization Solvent
3		White	192-194	86	Acetone
4		Yellow	190-191	73	Acetone
5		Brown	174-176	76	Ethanol
6		White	186-188	77	Dioxane
7		White	178-180	84	Acetone

8		White	182-183	85	Ethanol
9		White	184-186	82	Acetone
10		Brown	171-173	80	Ethanol
11		White	197-198	81	Acetone

Results and Discussion

Since both Schiff base and cyclic imide are important and valuble groups having wide spectrum of biological activities besides variety of applications, the aim of the present work is to synthesize a series of new molecules containing these two active groups with expected biological activity. The target of this work was achieved by many steps which are indicated in Scheme-1.



Scheme-1

The first step involved synthesis of N-(4-acetophenyl)succinamic acid (1) by reaction of succinic anhydride with 4-aminoacetophenone [11]. The reaction was proceeded through nucleophilic attack of amino group on carbonyl group in succinic anhydride leading to ring opening and producing of amic acid (1). Compound (1) was dehydrated in the second step by using acetic anhydride and anhydrous sodium acetate as a dehydrating agent [12]. Anhydrous sodium acetate catalyst abstract a proton from

amic acid (1) producing the corresponding sodium salt which attack carbonyl group in acetic anhydride followed by subsequent intramolecular nucleophilic attack leading to dehydration and ring-closure producing N-(4-acetophenyl) succinimide (2).

The third step in this work involved introducing of compound (2) in acid-catalyzed condensation with a variety of primary aromatic amines producing the target Schiff bases N-(4-succinimidyl)phenyl methyl benzylidene (3-11). In general Schiff bases are prepared by condensation between carbonyl compounds and primary amines but in the present work we synthesized a modified carbonyl compound bearing succinimide cycle then introduce it in condensation reaction with different primary aromatic amines producing new molecules carrying two active groups Schiff base and cyclic imide present together in the same molecule.

The reaction was proceeded through nucleophilic attack of amino group in aromatic amine on carbonyl group in compound (2) followed by abstraction of water and formation of imine group. Physical properties of Schiff bases (3-11) are shown in Table-1.

Chemical structures of the prepared compounds were confirmed on the bases of their FTIR spectral data besides ^{1}H-NMR and ^{13}C-NMR spectra for some of them.

FTIR spectrum of compound (1) showed two clear characteristic absorption bands at 3338 cm^{-1} and 3224 cm^{-1} which are due to ν(OH) carboxylic and ν(NH) amide. Absorption bands due to ν(C=O) carboxyl and ν(C=O) amide appeared at 1716 cm^{-1} and 1693 cm^{-1} while absorption bands belong to ν(C=C) aromatic and ν(C=O) ketone appeared at 1593 cm^{-1} and 1645 cm^{-1} respectively [18].

^{1}H-NMR spectrum of amic acid (1) showed singlet signal at δ=2.37 ppm and multiplet signal at (δ=2.42-2.6) ppm belong to CH_3 protons and (CH_2CH_2) imide protons. Signals appeared at (δ=(6.01-8.39)ppm belong to aromatic protons and two singlet signals appeared at(δ= 10.3 and 12.14) ppm belong to (NH) proton and (OH) proton respectively [18].

^{13}C-NMR spectrum of compound (1) showed signals at δ=(25.7-26.3) and (28.6-31.1) ppm which belong to CH_3 and (CH_2CH_2) carbons. Signals belong to aromatic carbons appeared at δ = (112.4-153.5) ppm and signals belong to (C=O) amide, (C=O) carboxyl group and (C=O) ketone appeared at δ= (170.7, 173.7 and 196.39) ppm respectively.

FTIR spectrum of compound (2) showed disappearance of absorption bands belong to ν(OH) carboxyl and ν(NH) amide and appearance of two bands at 1772 cm^{-1} and 1712 cm^{-1} due to asym. and sym. ν(C=O) imide. These two points are excellent proofs for success of imide formation. Absorption bands appeared at 1683 cm^{-1}, 1602 cm^{-1} and 1394 cm^{-1} are attributed to ν(C=O) ketone, ν(C=C) aromatic and ν(C-N) imide respectively.

^{1}H-NMR spectrum of compound (2) showed disappearance of (OH) carboxyl and (NH) amide signals and this is important proof for success of dehydration and imide formation. The spectrum showed also singlet signal at (δ=2.52) ppm and multiplet signal at (δ=2.61-2.81) ppm which are belong to CH_3 protons and (CH_2CH_2) imide protons and signals at (δ=7.45-8.4) ppm belong to aromatic protons.

^{13}C-NMR spectrum of compound (2) showed signals at δ= 24.11 and (26.32-29.15) ppm belong to CH_3 and (CH_2CH_2) imide carbons. Signals belong to aromatic carbons, (C=O) imide and (C=O) ketone carbons appeared at δ = (114.2-136.71), 176.54 and 197.24 ppm.

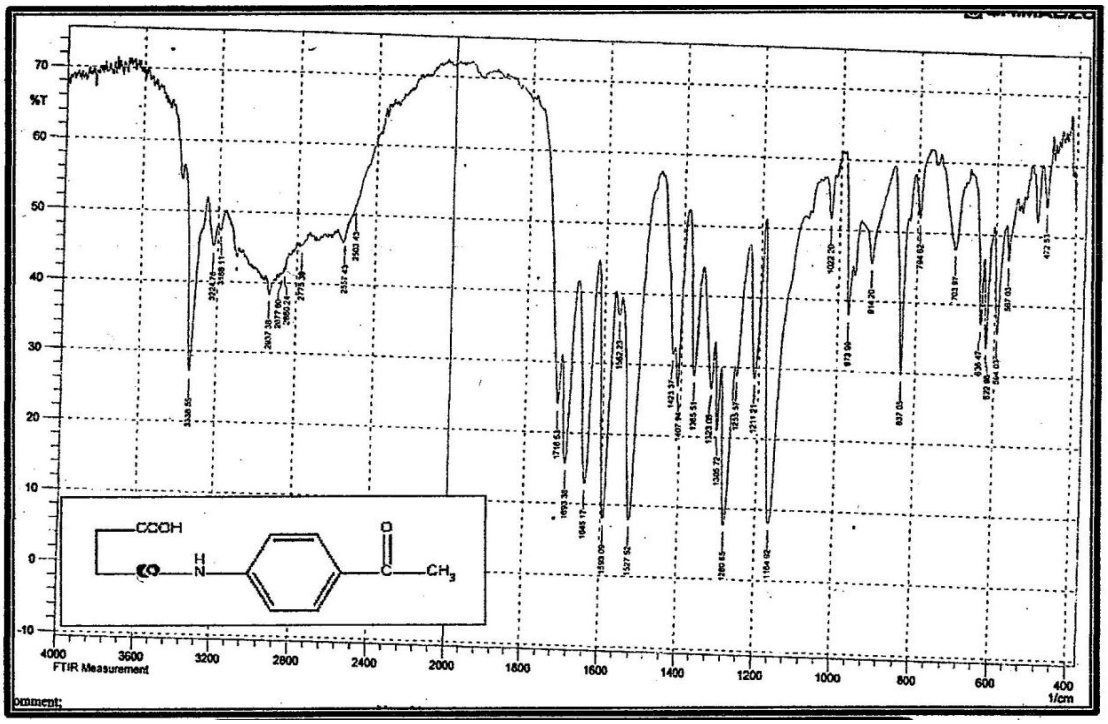


Figure 1- FTIR spectrum of compound (1).

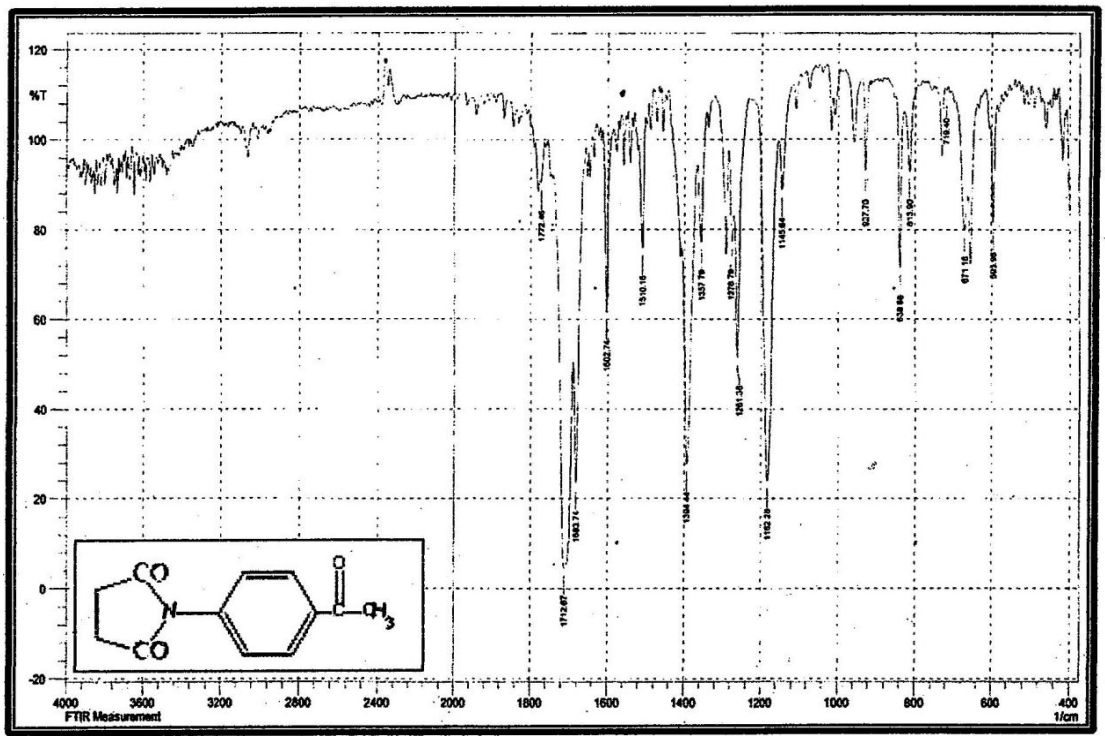


Figure 2- FTIR spectrum of compound (2).

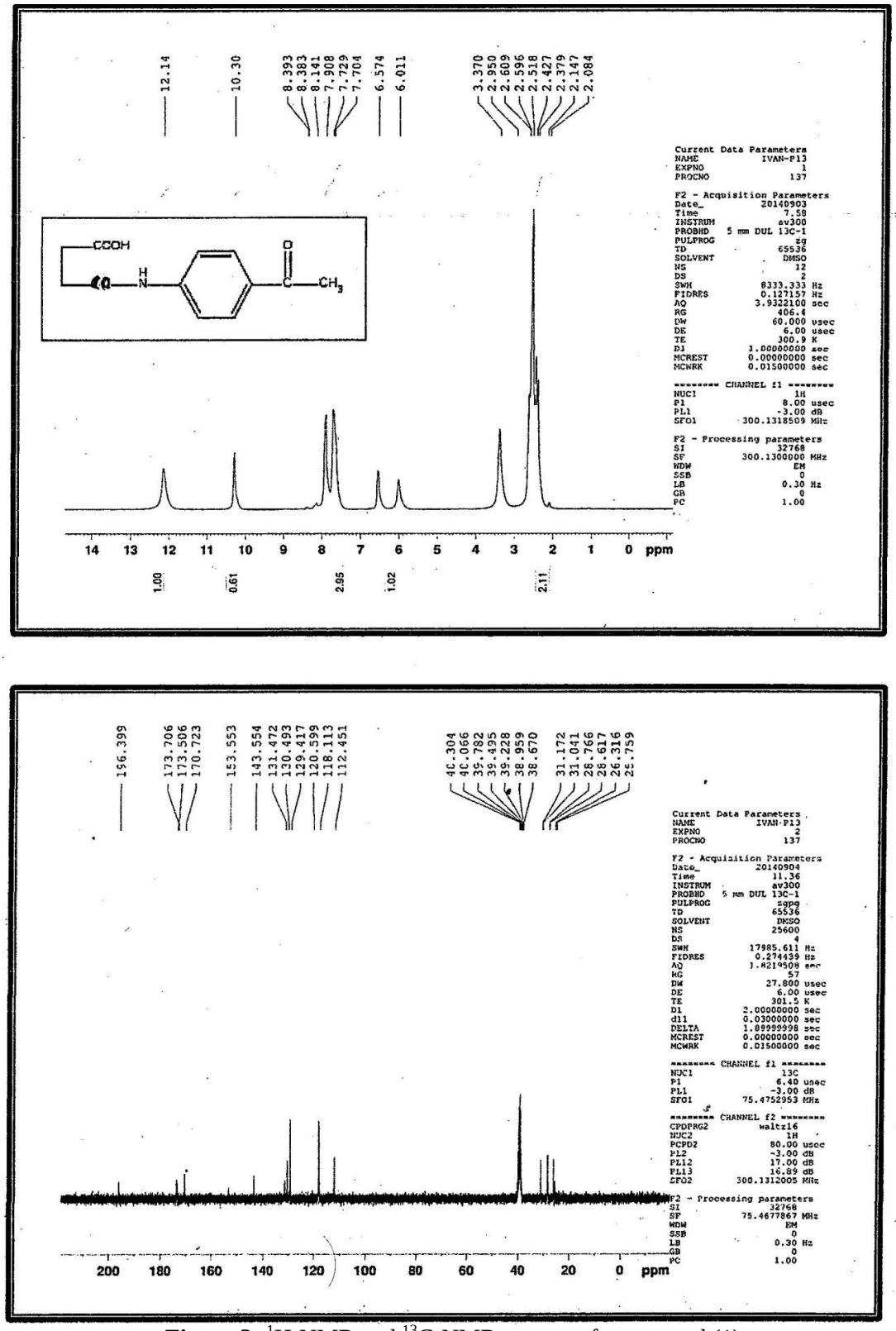


Figure 3- ^{1}H-NMR and ^{13}C-NMR spectra of compound (1)

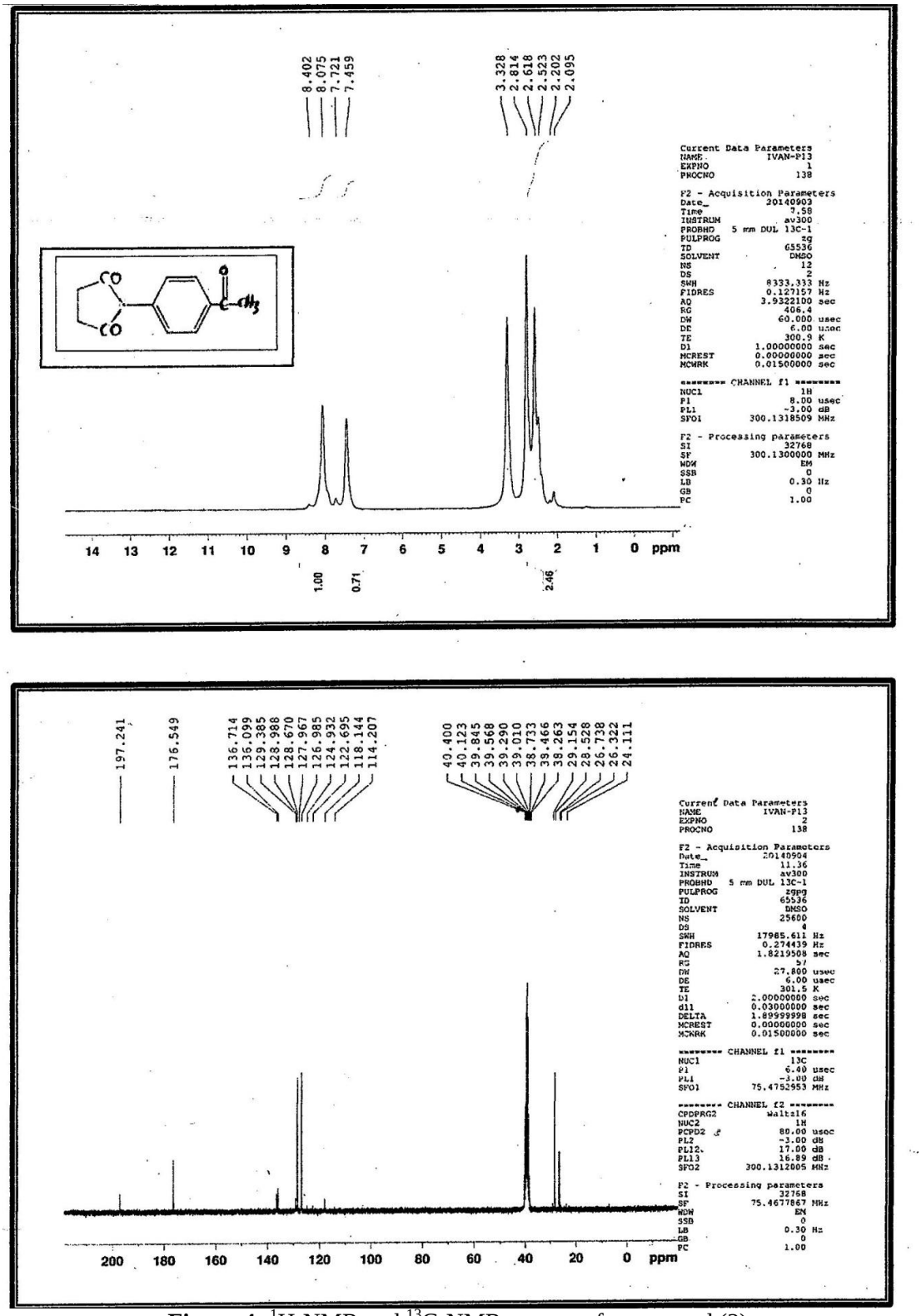


Figure 4- ^{1}H-NMR and ^{13}C-NMR spectra of compound (2).

FTIR spectra of Schiff bases (3-11) showed disappearance of ν(C=O) ketone absorption band at 1683 cm^{-1} and appearance of absorption bands at (1596-1676) cm^{-1} due to ν(C=N) imine. Other absorption bands appeared at (1720-1780) cm^{-1}, (1672-1715) cm^{-1}, (1548-1602) cm^{-1} and (1357-1398) cm^{-1} which are attributed to asym. ν(C=O) imide, sym. ν(C=O) imide, ν(C=C) aromatic and ν(C-N) imide respectively [18]. Other details of FTIR spectral data of Schiff bases (3-11) are listed in Table-2.

^{1}H-NMR spectrum of Schiff base (4) 4-(N-succinimdyl)phenyl methyl-4-nitrobenzylidene showed singlet signal at(δ = 2.51)ppm and multiplet signals at (δ=2.61-2.80) ppm belong to CH_3 and (CH_2CH_2) imide protons beside multi signals appeared at (δ = 7.09-8.21)ppm belong to aromatic protons.

^{13}C-NMR spectrum of Schiff base (4) showed signals at δ =17.38 and δ = (26.32-28.52) ppm belong to CH_3 and (CH_2CH_2) imide carbons. Other signals appeared at δ = (118.14-136.7) ppm, 168 and 176.55 ppm which are belong to aromatic carbons, (C=N) imine and (C=O) imide carbons.

^{1}H-NMR spectrum of Schiff base (5) 4-(N-succinimdyl)phenyl methyl-3-hydroxy benzylidene showed signals at δ = 2.36 and (2.5-2.6) ppm belong to CH_3 and (CH_2CH_2) imide protons. Signals for aromatic protons appeared at δ = (6.45-8.45)ppm while signal belong to phenolic (OH) proton was appeared at δ =5.15 ppm.

^{13}C-NMR spectrum of Schiff base (5) showed signals at δ =23.1 ppm and 29.4 ppm belong to CH_3 and (CH_2CH_2) imide carbons. Other signals appeared at δ = (105-138.1), 149.7 and 169.2 ppm which are belong to aromatic carbons, (C=N) imine and (C=O) imide carbons.

Table 2- FTIR spectral data (cm^{-1}) of Schiff bases (3-11)

Comp. No.	ν(C-H) aromatic	ν(C-H) aliphatic	ν(C=O) imide	ν(C=N) imine	ν(C=C) aromatic	ν(C-N) imide	Others
3	3045	2930	1778 1706	1629	1602	1390	-
4	3062	2923	1776 1699	1676 1645	1598	1392	ν(NO_2) 1500, 1342
5	3080	2923	1774 1706	1604	1558	1390	ν(O-H) phenolic 3460
6	3070	2954	1740 1715	1664	1600	1375	-
7	3060	2923	1720 1689	1598	1560	1370	ν(C-Cl) 1095
8	3080	2970	1730 1689	1596	1570	1357	ν(O-H) phenolic 3427
9	3060	2972	1715	1650	1598	1396	-
10	3024	2920	1740 1706	1652	1548	1369	ν(O-H) phenolic 3400
11	3081	2943	1780 1703	1637	1600	1398	ν(C-Cl) 1097

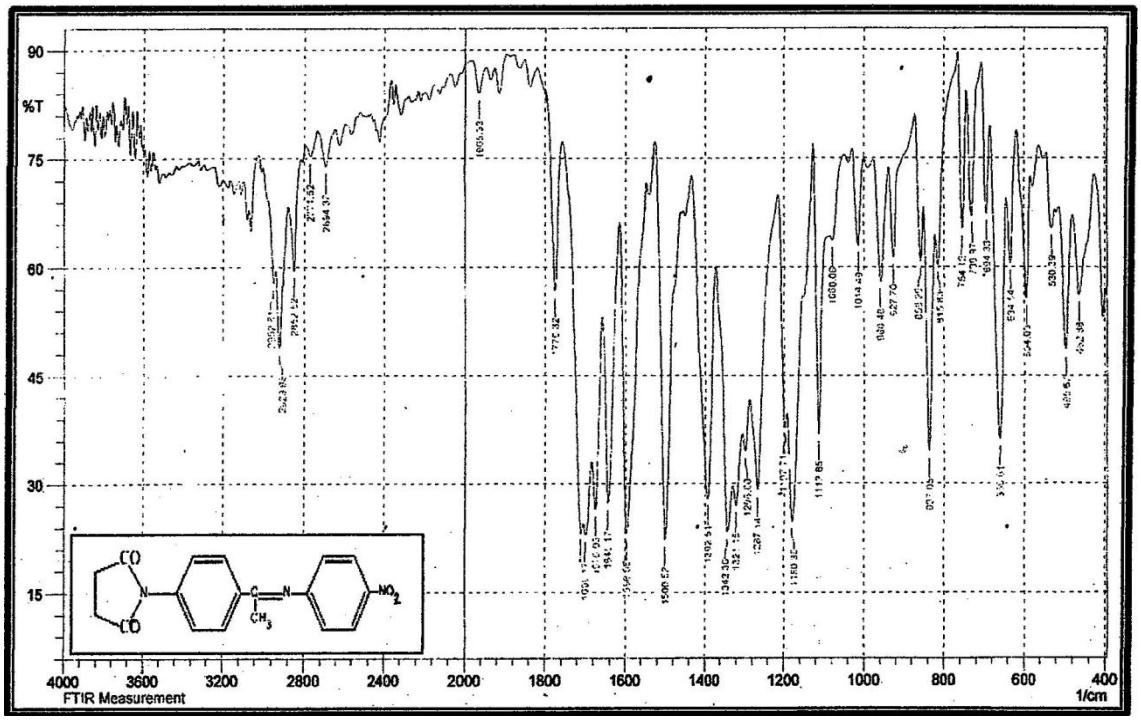


Figure 5- FTIR spectrum of compound (4).

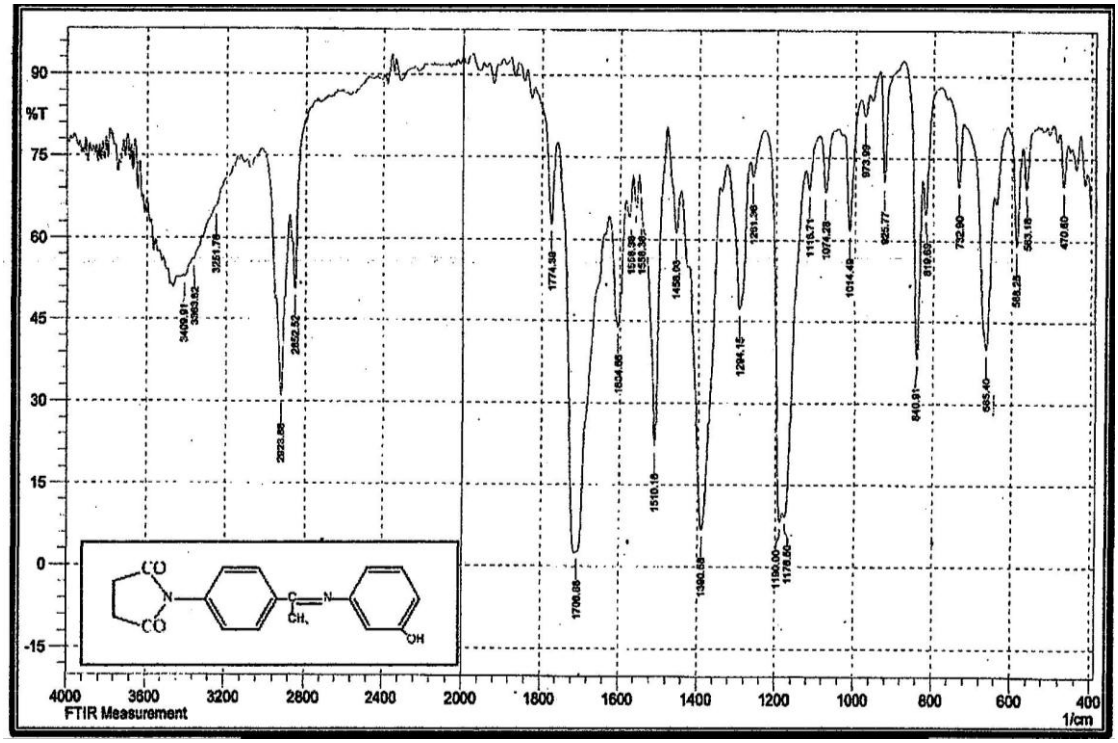


Figure 6- FTIR spectrum of compound (5).

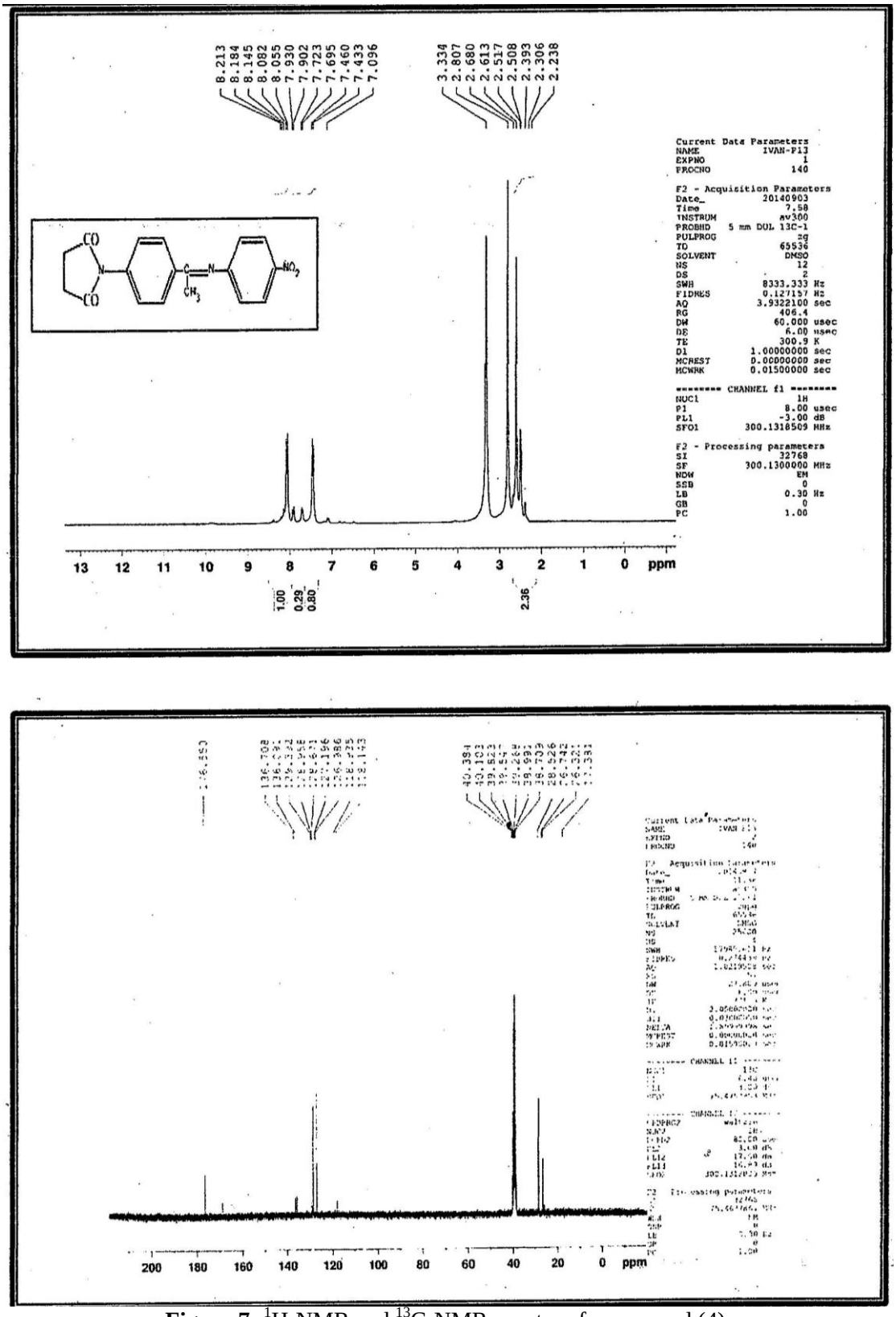


Figure 7- ^{1}H-NMR and ^{13}C-NMR spectra of compound (4).

Biological Activity

The prepared Schiff bases (3-11) are expected to possess biological activity since their molecules are built from two biologically active components thus antibacterial activity of Schiff bases (3-11) are tested against two types of Gram-positive bacteria *Staphylococcus aureus, Streptococcus pyogenes* and two types of Gram-negative bacteria *E. Coli* and *Pseudomonas aeroginosa.* The results indicated

that most of the prepared Schiff bases possess good antibacterial activity. Besides type of substituents present in Schiff base molecules play an important role in their antibacterial activities, thus Schiff bases (5, 8, 10) which are substituted with hydroxyl groups showed high antibacterial activity, Schiff bases (3, 9, 11) which are substituted with methyl group on phenyl ring showed moderate activity while Schiff bases substituted with chloro or nitro group showed slight activity. Inhibition zones for antibacterial activities are listed in Table-3.

Table 3- Antibacterial activity of Schiff bases (3-11)

Comp. No.	*S. aureus*	*S. pyogenes*	*E. Coli*	*P. aeuroginosa*
3	++	++	-	-
4	+	+	+	++
5	+++	++	+	+
6	+	+	-	-
7	+	+	-	-
8	+++	+++	++	+
9	++	++	+	++
10	+++	+++	++	+
11	++	+	++	+

Key to symbols: inactive (-) inhibitions zone < 6 mm
Slightly active (+) inhibition zone = 6-9 mm
Moderately active (++) inhibition zone = 9-12 mm
Highly active (+++) inhibition zone = 13-17 mm

Conclusion

Synthesis of new nine Schiff bases based on N-(4-acetophenyl)succinimide were preformed via introducing of this imide in condensation with different primary aromatic amines. The results of antibacterial screening showed that the new Schiff bases exhibit good antibacterial activity.

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