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Synthesis, Characterization, Biological Activity Studies of Schiff Bases and 1,3-Oxazipene Derived from 1,1 -Bis (4-aminophenyl) -4-Phenyl Cyclohexane

Olfat A. Nief*[1], Hussein N. Salman[1], Luma S. Ahamed[2]
[1]Department of Chemistry, College of Science, Al-Mustansiriyah University, Baghdad, Iraq.
[2]Department of Chemistry, College of Science, University of Baghdad, Baghdad, Iraq.

Abstract

A series of new Schiff bases and 1, 3-Oxazepine derivatives have been synthesised from condensation compound (1,1 -bis (4-aminophenyl) -4-phenyl cyclohexane [C1] with different aromatic aldehydes in the presence of catalytic glacial acetic acid to produce the Schiff bases [2-4]. These Schiff bases were reacted with maleic anhydride and phthalic anhydride in dry benzene to give seven-membered heterocyclic ring derivatives [5-10]. The structure formula of these compounds were confirmed by using FT-IR, (^{1}H and ^{13}C) NMR spectroscopy. The synthesized compounds were screened for their anti-bacterial activity using ampicillin as a standard drug.

Keywords: Schiff bases, Oxazepine, Diamine aromatic compound, Antibacterial activity.

تحضير و تشخيص ودراسة الفعالية البايولوجية لقواعد شيف و1و3-اوكسازايبن مشتقة من 1,1- ثنائي (4- امينو فنيل)-4- فنيل سايكلو هكسان

ألفة عبد نايف*[1]، حسين ناصر سلمان[1]، لمى سامي احمد[2]
[1]قسم الكيمياء، كلية العلوم ، الجامعه المستنصرية، بغداد، العراق
[2]قسم الكيمياء، كلية العلوم، جامعة بغداد، بغداد، العراق

الخلاصة

يتضمن البحث تحضير عدد من قواعد شف الجديدة ومشتقات 1،3- أوكسازابين بتكاثف المركب ثنائي 1,1[4-أمينوفينل]-4-فنيل سايكلوهكسان [C1] مع ألديهايدات اروماتية مختلفة بوجود حامض الخليك الثلجي كعامل مساعد بغرض الحصول على قواعد شيف [2-4]. و تم مفاعلة قواعد شيف هذه مع أنهدريد الماليك وأنهدريد الفثاليك في البنزين الجاف فأعطت مشتقات سباعية الحلقة غير متجانسة [5-10]. وتم تشخيص الصيغ التركيبية للمركبات المحضرة باستخدام أطياف FT-IR و NMR - (^{1}H و ^{13}C). و تم فحص المركبات التي تم تحضيرها كمضادات للبكتيريا باستخدام الأمبيسلين كدواء قياسي.

INTRODUCTION

The 1, 2-diamine fundamental idea is found in a wide range of compounds showing a wide spectrum of pleasant biologically activities. These compounds range from natural products, containing those that perform the functions of the basic metabolism within the human rights body; to synthetic products, which have become important medical factors in the treatment of a variety of diseases. The

*Email: Olfat_Nife@uomustansiriyah.edu.iq

importance of this simple functional group has further been proven with its application to asymmetric synthesis. There are a huge number of biologically active natural products that contain 1,2-diamines, many of which have been employed as medicinal agents for the treatment of a variety of diseases, for example 2,3-diaminopropanoic acids are found in a range of important compounds such as the glycopeptidicbleomycins, which are used as chemotherapeutic agents for the treatment of malignant lymphomas and squamous cell carcinomas and the well known penicillin-type antibiotics [1].1,2-diamines are the important constituents or intermediates in dyes, agrochemicals, varnish, coating, pesticides, fertilizers, etc. They are useful in manufacturing thermally stable polyimides, epoxy resins, formaldehyde resins [2]. A Schiff base is a nitrogen correspondent of an aldehyde or ketone in which the C=O group is exchanged by C=N-R group [3]. It is prepare by reaction of an aldehyde or ketone with a primary amine. The chemistry of (C=N) group has played asanimated role in the progress of chemical sciences, due to the presence of a lone pair of electrons on the nitrogen atom and the general electron donating character of the double bond. These compounds have very large applications in the field of chemistry [4] of which as fine chemicals medical substrates or as a starting material in the synthesis of important drugs, such as antibiotic, anti- allergic, anticancer, antiphlogistic and antitumor, etc. [5-7]. Analytical reagents and ligands for metal complexes having industrial importance as an asymmetric catalysis [8- 13]. In this paper we have prepared new Schiff bases and heterocyclic derivatives of 1, 1-bis (4-aminophenyl) -4-phenyl cyclohexane because these compounds have many applications in medicine and industry.

Experimental

1) Chemicals

All chemicals used in the prepare compounds were supplied from Aldrich Chemicals and its used without further purification. All melting points were taken in open capillary tube and are uncorrected by Gallenkamp capillary melting point apparatus. The purity of the compounds was checked by TLC on pre-coated SiO_2 gel (HF254, 200 mesh) aluminum plates (E Merk) using Butanol: Acetic acid: water (4:1:5) visualized in iodine chamber. FTIR spectra were recorded with Shimadzu (8400S) spectrophotometer. The ^{1}H ,^{13}C-NMR were determined with Bruker Spectrophotometer model ultra-shield at 300 MHz in DMSO -d_6 solution with the TMS as a standardinternal .

2) Methods of synthesis

1) Synthesis ofcompound (1, 1 -bis (4-aminophenyl) -4-phenyl cyclohexane C1)

The compound (1,1¯bis (4-aminophenyl) -4-phenyl cyclohexane C1) was synthesized by using autoclave made from stainless steel with a volume of 300 ml and 12.5 cm diameter as shown in Figure-1 [14-17].

Figure 1- Autoclave apparatus.

0.23 mole (29.3ml) aniline, (1ml) hydrochloric acid and (0.10 mole ,17.4gm)4-phenyl cyclohexanone. The mixture was transferred into Autoclave and then closed it very well to ensure getting a high temperature and pressure. This system was heated in oil bath at 120^{o}C for 2hrs., and then at 140-150 ^{o}C for 9hrs., Then the resulted mixture was placed in a beaker, The resultant solution of 1,1^{-} -bis (4-aminophenyl) -4-phenyl cyclohexane was cooled to 120^{o}C and (50 ml) as boiling water was added to get solution.The solution was made alkaline by using 10% NaOH solution to remove unreacted aniline. The compound (C1) was filtered, washed well with distilled water and dried in an oven at 50^{o}C.The product compound is recrystallized repeatedly from benzene, n- hexane, the purity of compound (C1) was checked by TLC. Table (1) showed the nameand structural formula of compound.

1,1^{-} - bis (4-aminophenyl) -4-phenyl cyclohexane (C1)

The yield: 68%:Gray greenish, M. p :110-112 °C: recrystallization solvent (benzene, n-hexane), FTIR (υ, cm^{-1}) [18, 19]: 3348, 3209 υ(NH_2) symmetric and asymmetric, 1618 υ (N-H deformation) [20], 3057,3026 υ(CH aromatic), 2922,2860 υ(CH aliphatic), 1579,1512 υ(C=C aromatic), 1278υ (C–N), 825,759.704 υ(CH out of plane for para and mono substituted phenyl) [Figure- 2]: ^{1}H-NMR (300 MHz, DMSO-d_6, δ, ppm): 7.7- 6.9 (m, 8H, Ar-H), 6.7 (singlet, 4H, NH_2), 1.6-2.7 (m, 9H, cyclohexyl ring) [Figure-3]: ^{13}C-NMR DMSO- d_6): 29,33,34,42 (C-cyclohexyl ring), 115-129 (C aromatic ring), 149 (C-NH_2), [Figure-4].

2) Synthesis of Schiff bases (C 2-4) [5]

Compound C1 (0.342g, 0.001mol) was taken in a 100ml single necked round bottom flask, 10mL of absolute ethanol and substituted aromatic aldehyde (0.002mol) in (20ml) absolute ethanol and two drops of glacial acetic as a catalyst was added. The reaction mixture was refluxed for (8 -12 hrs). The solvent was removed under reduced pressure to offer the product. The Schiff bases were recrystallized repeatedly from appropriate solvent systems and their purity was checked by TLC in appropriate solvent system at room temperature. Table (1) showed names and structural formula of the prepared compounds.

2,2'-((4-phenylcyclohexane-1,1-diyl)bis(4,1-phenylene))bis(azanylylidene))bis(methanylylidene)) diphenol (C2)

The yield: 50% : pale green, M. p: 179-181°C;recrystallization solvent (Chloroform) FTIR (υ, cm^{-1}): 3026 υ(CH aromatic), 2943, 2854 υ(CH aliphatic), 1614 υ(CH=N), 1595, 1570, 1492 υ(C=C aromatic), υ(OH hydrogen bonding with imine group) [20]), 1402 υ (O–Hdef.),1174 υ (C– O str.), 1363. υ(C – N), 827, 752, 786, 700 υ(CH out of plane for ortho, para and mono substituted phenyl) [Figure-5].^{1}H-NMR spectrum of compound (C2) showed clear signals at δ= 1.5-4.2 ppm due to protons of (cyclohexyl ring), multiplet signals at δ= (6.5-8.7) ppm for aromatic protons, signals at δ= 8.90 ppm, 8.99ppm for imine proton (-N=CH-) and OH [Figure-6].While ^{13}C-NMR spectrum of the same compound showed signal at δ = (30, 36, 42, 44) ppm (C-cyclohexyl ring), signals at δ= (116-149) ppm for aromatic carbons, signal at δ= 158 ppm (C-OH) and signal at δ= 163ppm (C=N) [Figure-7].

4,4'- ((4-phenylcyclohexane -1,1 -diyl) bis (4,1-phenylene)) bis (azanylylidene)) bis (methanylylidene)) bis (N,N-dimethylaniline) (C3)

The yield: 57%: yellow greenish, M. p: 220-222 °C: recrystallization solvent (ethanol) FTIR (υ, cm^{-1}): 3076, 3051 υ(CH aromatic), 2922, 2852 υ(CH aliphatic), 1604 υ(CH=N), 1585, 1552 υ(C=C aromatic), 1365 υ(C– N), 839, 819, 736, 698 υ(CH out of plane for para and mono substituted phenyl) [Figure- 8]:^{1}H-NMR spectrum of compound (C3) showed clear signals at δ= 1.5-3.5 ppm due to protons (cyclohexyl ring), multiple signals at δ= (6.4- 7.9) ppm for aromatic protons and signal at δ= 8.2 ppm for imine (-N=CH-), singlet signal at δ= 2.24 ppm due to protons (CH_3) proton [Figure- 9].

4, 4'-((4-phenylcyclohexane-1,1-diyl)bis(4,1-phenylene))bis(azanylylidene))bis(methanylylidene)) dibenzaldehyde (C4)

The yield: 56 %: pale olive, M.p:195-197 °C: recrystallization solvent (ethanol): FTIR (υ, cm^{-1}): 3080,3057,3026 υ (CH aromatic), 2926, 2935, 2858 υ (CH aliphatic),1756 υ (H aldehyde), 1701 υ(C=O), 1622 υ(CH=N), 1599, 1564, 1494 υ(C=C aromatic), 1300 υ(C– N), 879,873,758.698 υ(CH out of plane for ortho, Para, and mono substituted phenyl) Figure-10.

3) Synthesis of 1, 3- oxazepine ring derivatives (C5-10)

A mixture of Schiff bases derivative (C2-4) (0.0015 mole) and (phthalic anhydride), maleic anhydride (0.0025 mole) was melted in (20mL) solvent (dry benzene). The mixture was stirred and refluxed at

9-10 hrs. Excess solvent was distilled; The resulting solid crystals were filtered and recrystallized from solvents. Table (1) showed names and structural formula of the compounds.

3,3'-((4-phenylcyclohexane-1,1-diyl)bis(4,1-phenylene))bis(2-(2-hydroxyphenyl)-2,3-dihydro-1,3-oxazepine-4,7-dione) (C5)

The yield: 50%; dark green, M. p: 147-149°C; recrystallization solvent (Dioxan) FTIR (υ,cm^{-1}): 3080,3026 υ (CH aromatic), 2956,2856 υ (CH aliphatic), 1595, 1575 υ (C=C aromatic), 3346-3200 υ(OH broad), 1664 υ (C=O lactam), 1714 υ(C=O lactone), 1402 υ(O– H def.), 1151 υ(C – O str.), 1280 υ(C – N), 831, 758, 700 υ(CH out of plane for para, ortho and mono substituted phenyl) Figure-11.

4,4'-((4-phenylcyclohexane-1,1-diyl)bis(4,1-phenylene))bis(3-(2-hydroxyphenyl)-3,4-dihydrobenzo[e][1,3]oxazepine-1,5-dione) (C6)

The yield: 50%; dark green, M.p: 100-103°C; recrystallization solvent (Dioxan), FTIR (υ, cm^{-1}): 3057, 3014 υ (CH aromatic), 2956, 2854 υ(CH aliphatic), 1597, 1573 υ (C=C aromatic), 3346-3200 υ(OH broad), 1677 υ (C=O lactam), 1722 υ (C=O lactone), 1377 υ(O–H def.), 1118 υ(C–O str.), 1253 υ(C – N), 871, 756, 700 υ(CH out of plane for para, ortho and mono substituted phenyl) [Figure- 12].

3,3'-((4-phenylcyclohexane-1,1-diyl) bis (4,1-phenylene))bis(2-(4-(dimethylamino)phenyl)-2,3-dihydro-1,3-oxazepine-4,7-dione) (C7)

The yield: 58% : nutty bold, M. p. 78-80: °C; recrystallization solvent (THF). FTIR (υ,cm^{-1}): 3051 υ (CH aromatic), 2918, 2864 υ(CH aliphatic), 1593, 1539 υ (C=C aromatic), 1662 υ(C=O lactam), 1716 υ (C=O lactone), 1165 υ(C–O str.), 1230 υ (C – N), 817, 727, 700 υ(CH out of plane for para, ortho and mono substituted phenyl) [Figure- 13].

4,4'-((4-phenylcyclohexane-1,1-diyl)bis(4,1-phenylene))bis(3-(4-(dimethylamino)phenyl)-3,4-dihydrobenzo[e][1,3]oxazepine-1,5-dione) (C8)

The yield: 58%: nutty pale, M. p: 118-120 °C; recrystallization solvent (THF). FTIR (υ,cm^{-1}) : 3064, 3041 υ (CH aromatic), 2937, 2920, 2860 υ (CH aliphatic), 1597, 1579 υ (C=C aromatic), 1651υ (C=O lactam), 1724 υ (C=O lactone), 1167 υ(C–O str.), 1230 υ(C–N). 817, 783, 734, 700 υ(CH out of plane for ortho, Para and mono substituted phenyl) [Figure- 14].

4,4'-((4-phenylcyclohexane-1,1-diyl)bis(4,1-phenylene))bis(4,7-dioxo-2,3,4,7-tetrahydro-1,3-oxazepine-3,2-diyl))dibenzaldehyde (C9)

Yield: 58%; dark green, M.p 90-92 °C; recrystallization solvent (THF). FTIR (υ, cm^{-1}): 3088,3058υ (CH aromatic), 2752 υ(H aldehyde) 2972,2864 υ(CH aliphatic),1599,1494 υ (C=C aromatic), 1656υ (C=O lactam), 1732 υ (C=O lactone), 1174υ (C – O str.) , 1201 υ(C – N). 837, 758,.698 υ(CH out of plane for ortho, para and mono substituted phenyl) [Figure -15].

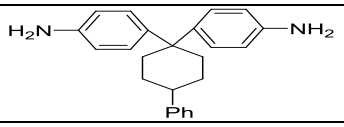
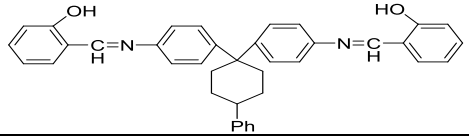
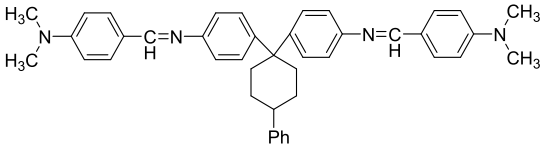
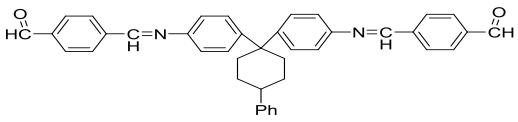
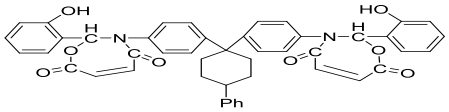
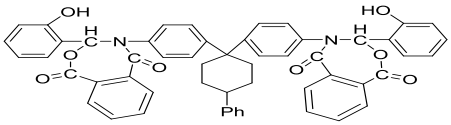
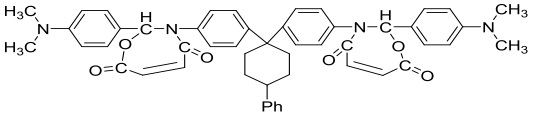
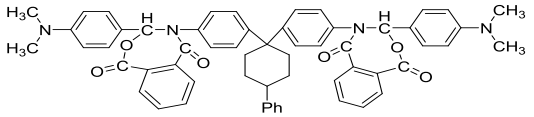
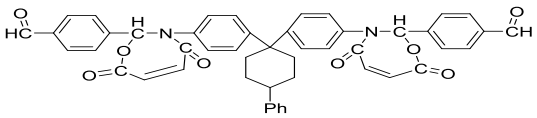
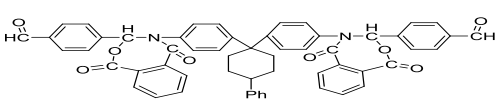
4,4'-(4-phenylcyclohexane-1,1-diyl) bis (4,1-phenylene)) bis (1,5-dioxo-1,3,4,5- tetrahydrobenzo [e][1,3]oxazepine-4,3-diyl))dibenzaldehyde (C10)

The yield: 58%; pale green, M.p ; 154-156 °C; recrystallization solvent (THF). FTIR (ν, cm^{-1}): 3066, 3022 υ(CH aromatic), 2928, 2858 υ(CH aliphatic), 1589, 1537, 1510 (C=C aromatic), 1662 υ(C=O lactam), 1703 υ(C=O lactone), 1199 υ(C–O str.), 1261 υ(C–N). 842, 696 υ(CH out of plane for ortho, para and mono substituted phenyl) Figure-16.

4) Antibacterial activity

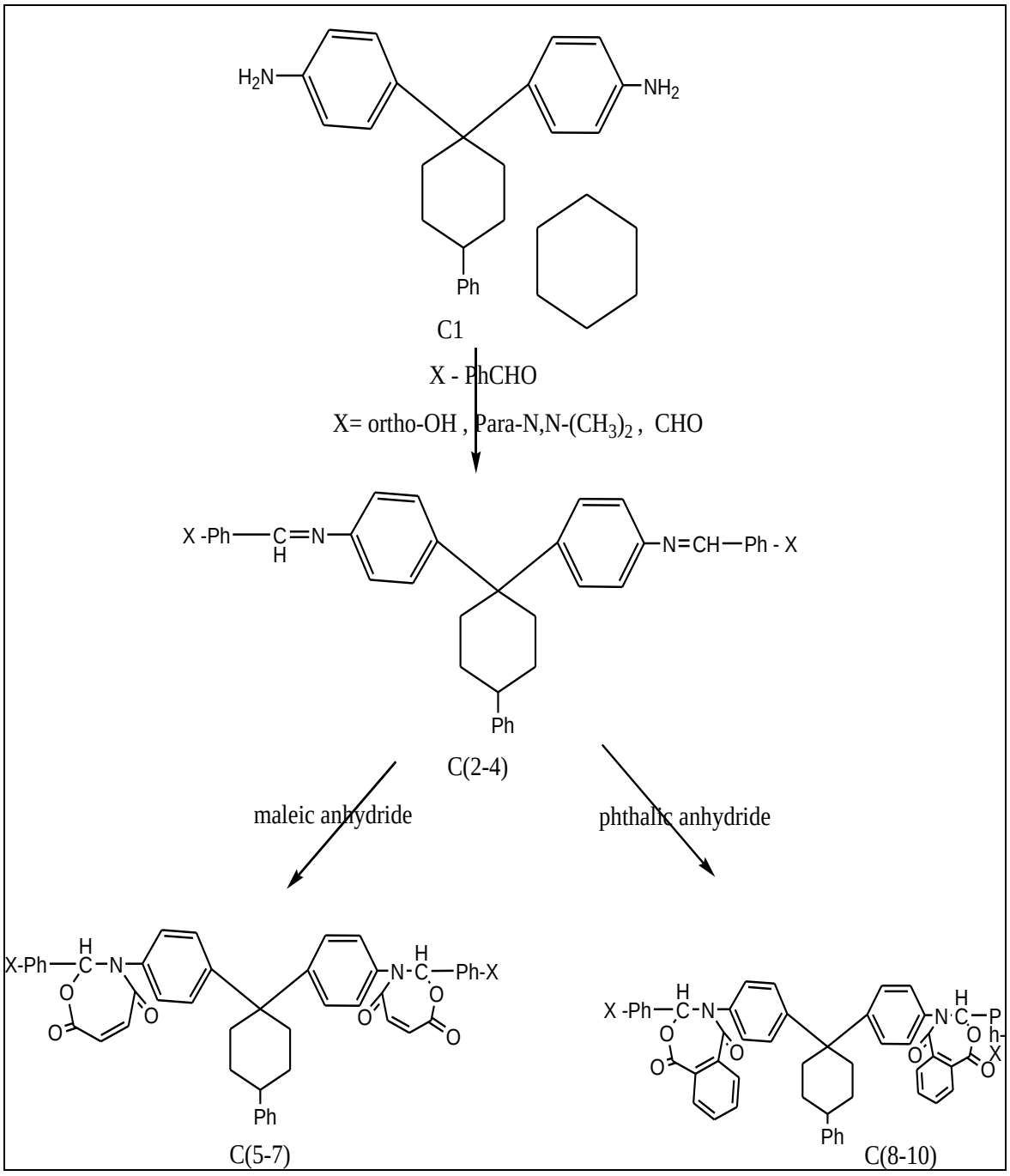
The samples were supplied by dissolving (1mg) of each compound in (1ml) of DMSO (dimethyl sulfoxide) as a control. Agar plates were prepared for propagation tests against bacteria using medium agar.Plates were incubated later at 37 °C. In the positive reactions, it observed appearance of zones of inhibition about the disks.compounds were checked for their anti-microbial activity. The inhibition of microorganism under standardized condition was utilized to demonstrate antimicrobial action of these compounds. In this workperformance of 10 compounds were detected against *S. aureus, S. pyogenes (G+), K.pneumonia, E. coli (G-).* The concentration of the test compound used was (1mg/ml) and Ampicillin was taken as the standard compound. All the synthesized compounds were screened *in vitro* for antibacterial activity against *S. aureus, S. S.pyogenes, K.pneumoniaaeruginosa, E.coli* using disc diffusion method at 1mg/ml disc concentration, Ampicillin (18-23 mm, zone of inhibition), DMSO (dimethyl sulphoxide) was taken is used as a solvent control [21-23].

Table 1- The name and structural formula of the prepared compounds.

Symbol compound	Name of compound	Structural formula of compound
C1		1,1- - bis (4-aminophenyl) -4-phenyl cyclohexane
C2		2,2'-((((4-phenylcyclohexane-1,1-diyl)bis(4,1-phenylene))bis(azanylylidene))bis(methanylylidene)) diphenol
C3		4,4'-((((4-phenylcyclohexane-1,1-diyl)bis(4,1-phenylene))bis(azanylylidene))bis(methanylylidene))bis (N,N-dimethylaniline)
C4		4,4'-((((4-phenylcyclohexane-1,1-diyl)bis(4,1-phenylene))bis(azanylylidene))bis(methanylylidene)) dibenzaldehyde
C5		3,3'-((4-phenylcyclohexane-1,1-diyl)bis(4,1-phenylene))bis(2-(2-hydroxyphenyl)-2,3-dihydro-1,3-oxazepine-4,7-dione)
C6		4,4'-((4-phenylcyclohexane-1,1-diyl)bis(4,1-phenylene))bis(3-(2-hydroxyphenyl)-3,4-dihydrobenzo[e][1,3]oxazepine-1,5-dione)
C7		3,3'-((4-phenylcyclohexane-1,1-diyl)bis(4,1-phenylene))bis(2-(4-(dimethylamino)phenyl)-2,3-dihydro-1,3-oxazepine-4,7-dione)
C8		4,4'-((4-phenylcyclohexane-1,1-diyl)bis(4,1-phenylene))bis(3-(4-(dimethylamino)phenyl)-3,4-dihydrobenzo[e][1,3]oxazepine-1,5-dione)
C9		4,4'-(((4-phenylcyclohexane-1,1-diyl)bis(4,1-phenylene))bis(4,7-dioxo-2,3,4,7-tetrahydro-1,3-oxazepine-3,2-diyl))dibenzaldehyde
C10		4,4'-(((4-phenylcyclohexane-1,1-diyl)bis(4,1-phenylene))bis(1,5-dioxo-1,3,4,5-tetrahydrobenzo[e][1,3]oxazepine-4,3-diyl))dibenzaldehyde

5 Results and Discussion

The structures formal of the new prepared compounds were shown in scheme- 1.



Scheme 1-Structures formal of the new prepared compounds.

The 1, 1' bis (4-aminophenyl) -4-phenyl cyclohexane is prepared according to literature [14-17]. Compound (**C1)** is identified by physical properties, FT-IR and ^{1}H,^{13}C -NMR spectroscopy. The FT-IR spectrum of compound (**C**1) shows clear absorption bands at υ (3348, 3209) cm^{-1}, due to symmetrical and asymmetrical bands for (NH_2) group. The ^{1}H-NMR spectrum in DMSO-d_6 as a solvent shows the following data: υ = 7.7- 6.9 (m, 8H, Ar-H), υ = 6.7 (singlet, 4H, NH_2), υ = 1,6-2.7(m, 9H, cyclohexyl ring).The ^{13}C-NMR spectrum in DMSO- $d_6$as a solvent shows the following data: 29.,33,34,42 (C-cyclohexyl ring), 115-129 (C aromatic ring), 149 (C-NH_2).

Schiff bases [C 2-4] were synthesized by condensation of one mole of aromatic primary amines (C1) with two moles of benzaldehyde derivative in the presence of two drops of glacial acetic acid as catalyst in absolute ethanol. Schiff bases (C2-4) is identified by physical properties, FT-IR and ^{1}H, ^{13}C -NMR spectroscopy. The FT-IR spectra of these bases showed disappearance of absorption bands at

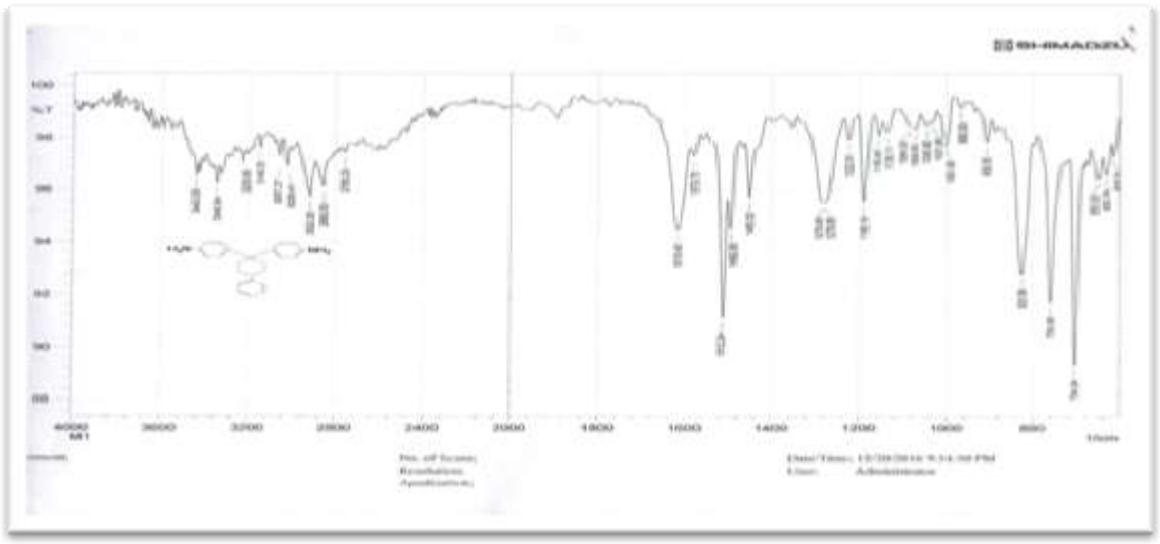


Figure 2- FT-IR spectrum of (C1).

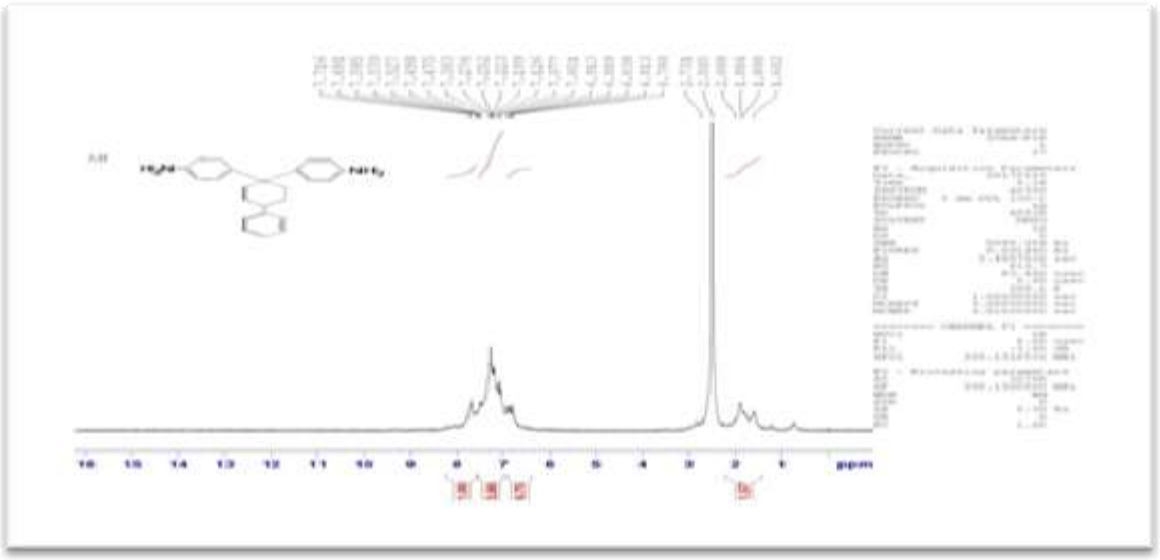


Figure 3- ^{1}H-NMR spectrum of (C1).

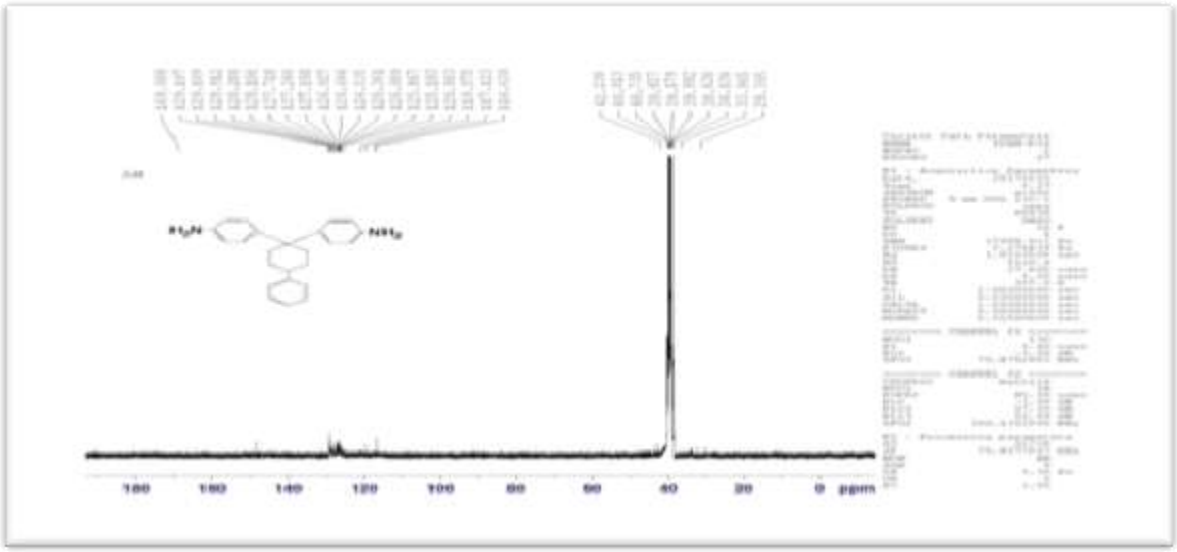


Figure 4- ^{13}C-NMR spectrum of compound (C1).

υ (3348, 3209) cm^{-1}) which belonging to (-NH_2) group and presence of new absorption bands at υ (1622-1604) cm^{-1}due to isomethane (C=N) group.^{1}H-NMR spectra of these bases in DMSO-d_6 as a solvent show the following data signals at δ= 1.5 -4.2 ppm due to protons of (cyclohexyl ring), multiplet signals at δ= (6.4- 8.7) ppm for aromatic protons and signals at δ= 8.2-8.9 ppm for imine proton (N=CH).^{13}C-NMR spectrum of compound (C2) showed signal at δ= (30, 36, 42, 44) ppm (C-cyclohexyl ring), signals at δ= (116-149) ppm for aromatic carbons, signal at δ= 158 ppm (C-OH) and signal at δ= 163 ppm for (C=N)**.**

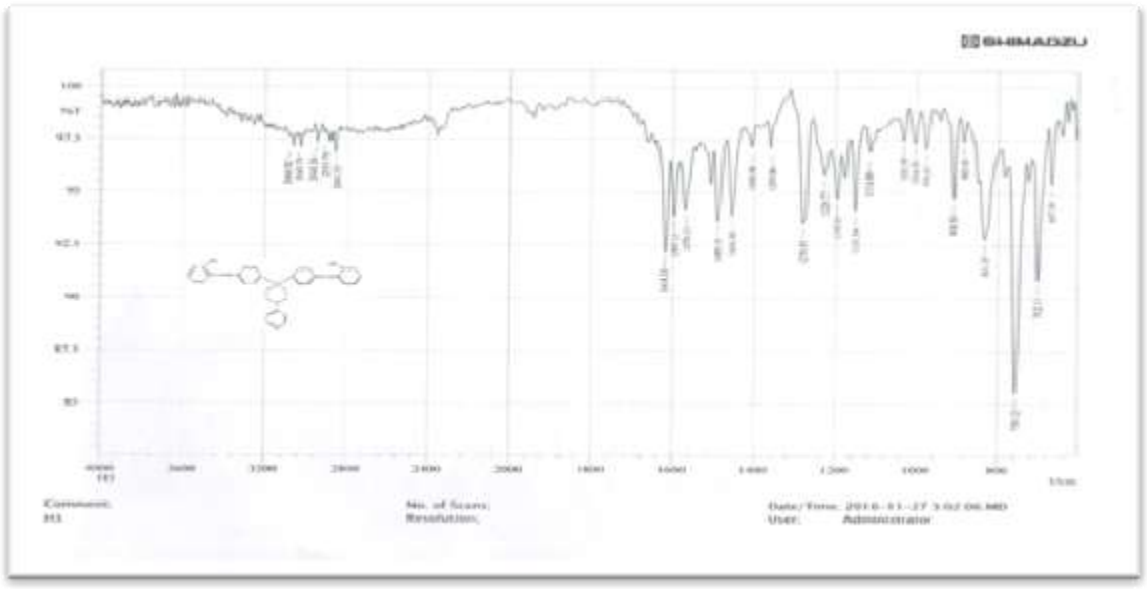


Figure 5- FT-IR spectrum of (C2).

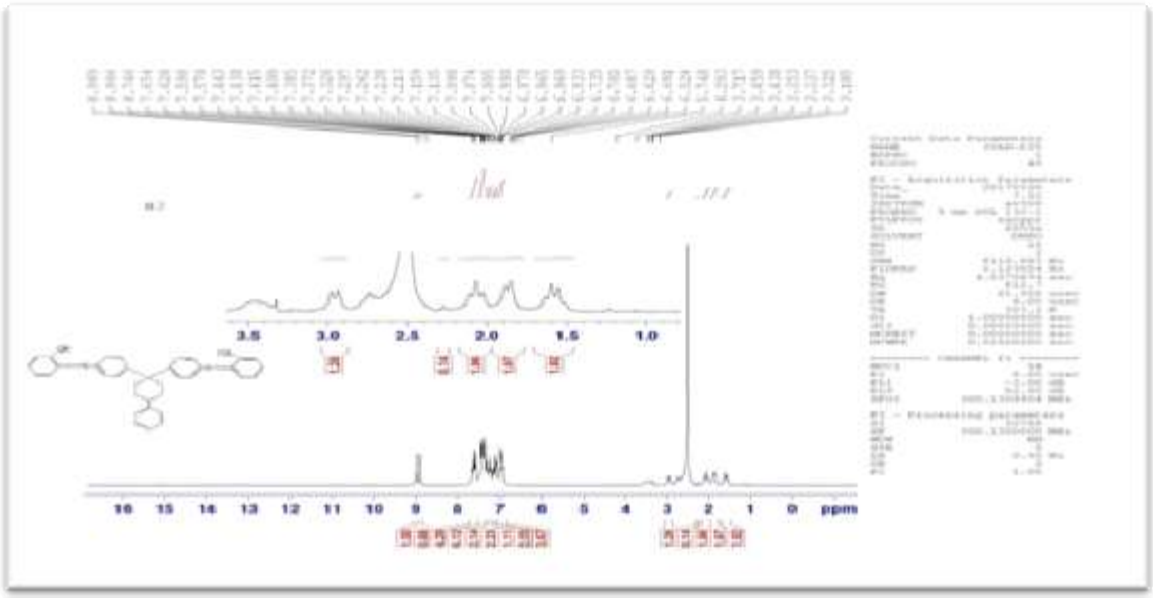


Figure 6- ^{1}H-NMR spectrum of (C2).

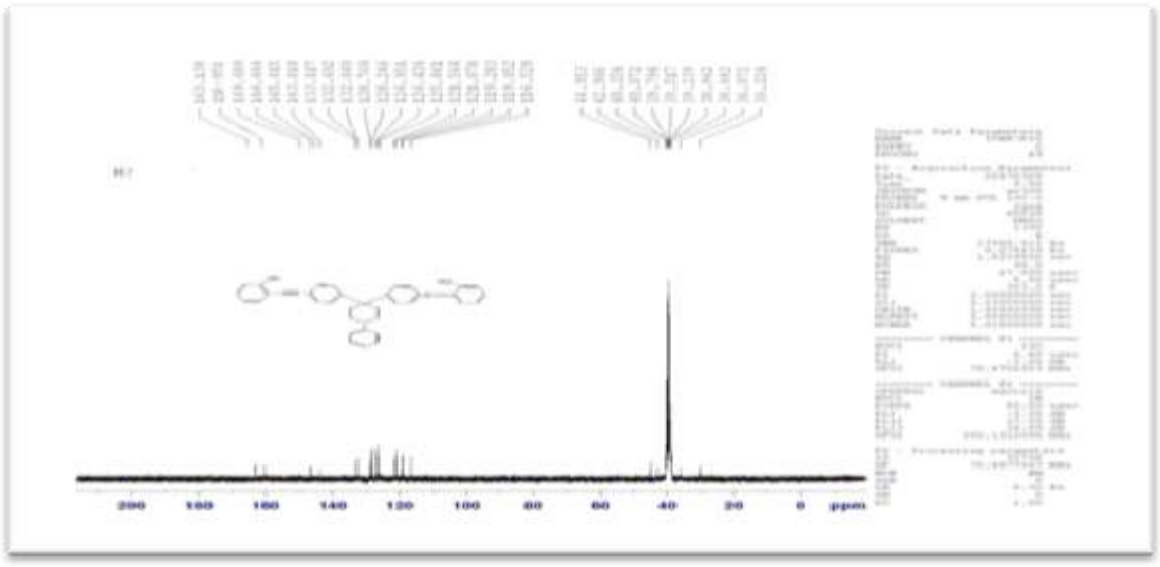


Figure 7- ^{13}C-NMR spectrum of compound (C2).

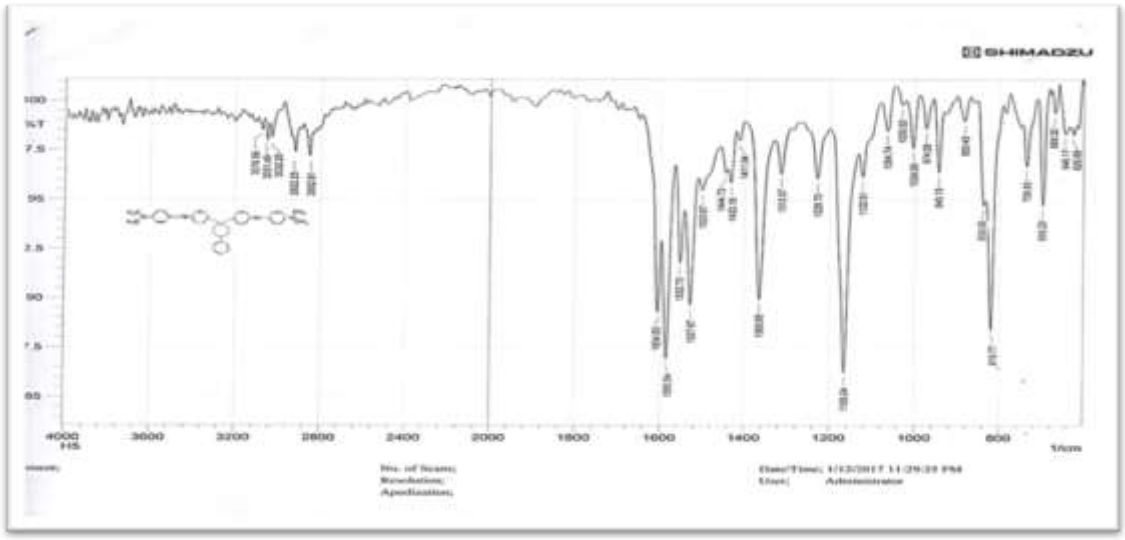


Figure 8- FT-IR spectrum of compound (C3).

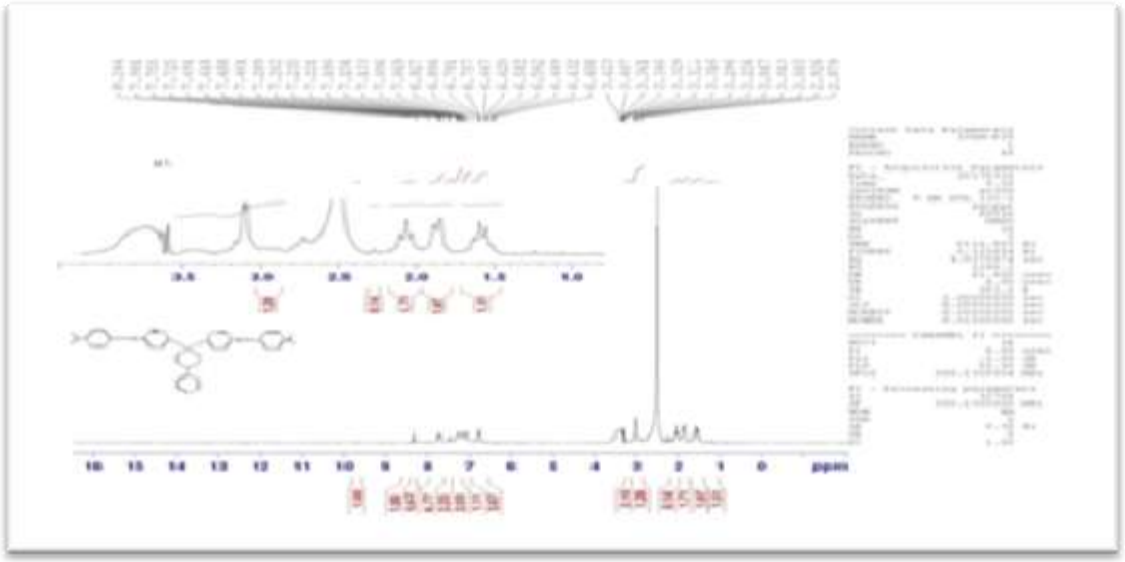


Figure 9- ^{1}HNMR spectrum of compound (C3).

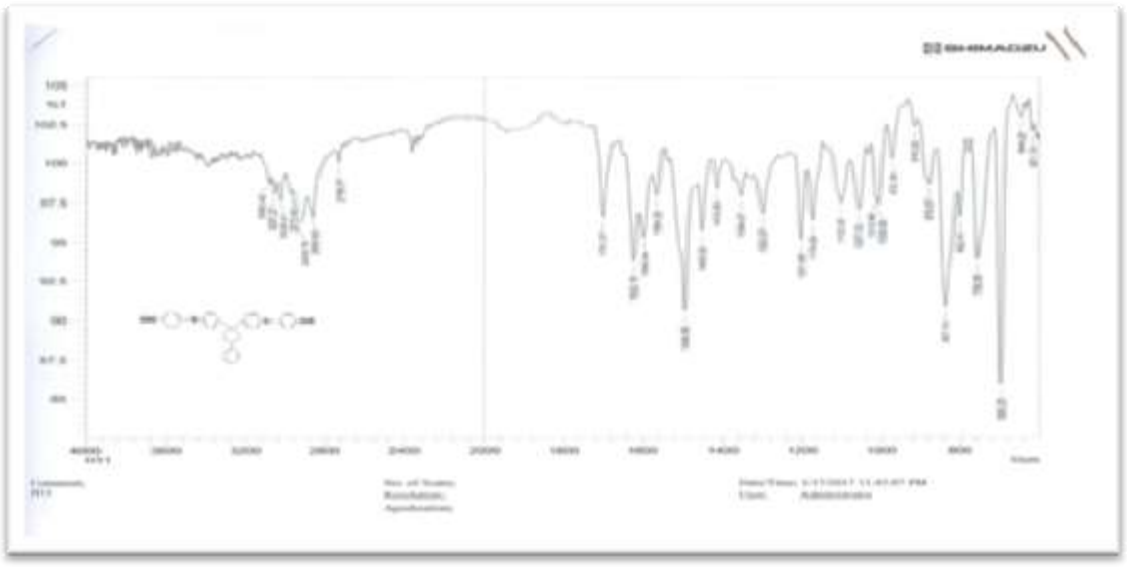
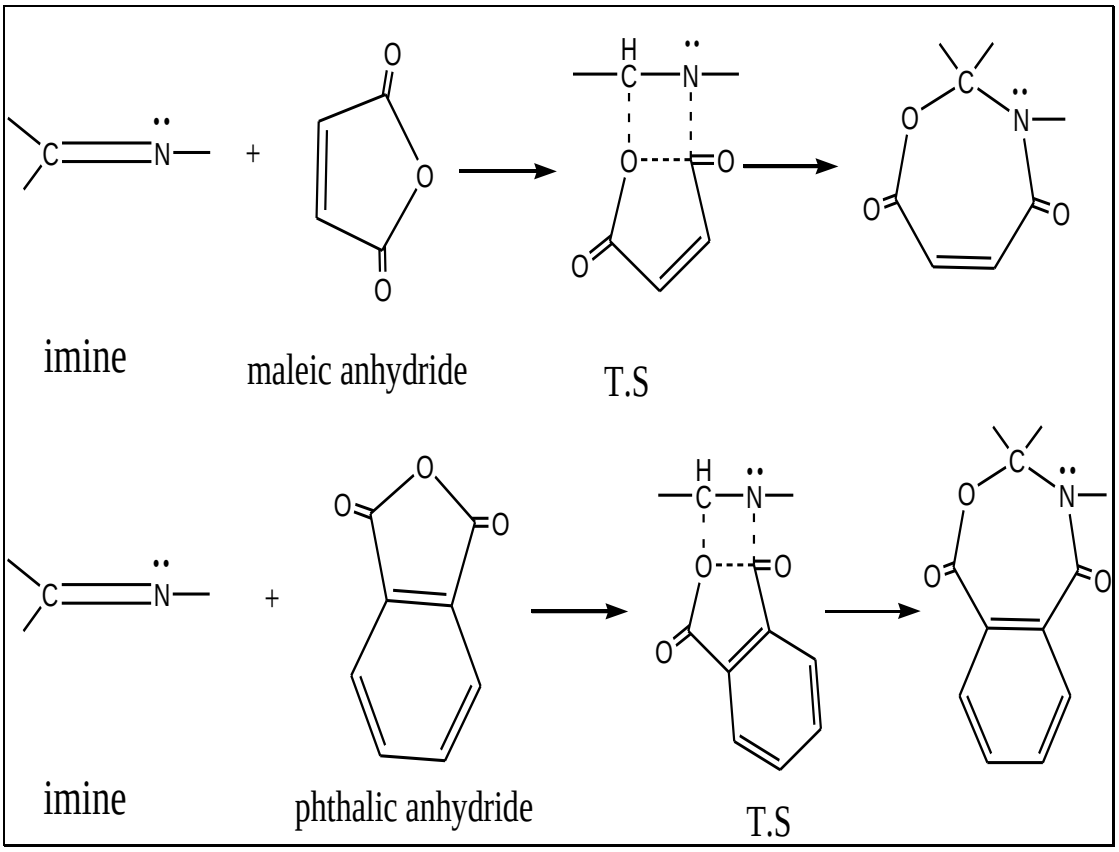


Figure 10- FT-IR- spectrum of compound (C4).

Pericyclic reactions, between imine groups of Schiff bases (C2-4) and cyclic acid anhydride [maleic anhydride and phthalic anhydride] in dry benzene, were carried out to synthesis of 1, 3-oxazepine derivatives (C5-10). Scheme (2) shows mechanism of the pericyclic reaction for the synthesis of 1, 3-oxazepine compounds [23].



Scheme-2 Mechanism of synthesised 1, 3-oxazepine.

Oxazepine compounds (C5-10) are identified by physical properties and FT-IR spectra. FT-IR [19, 20] spectra of oxazepines compounds showed the appearance of absorption bands at υ(1732-1703) cm^{-1} and υ(1651-1662) cm^{-1} for υ(C=O rings) of lactone and lactam respectively.

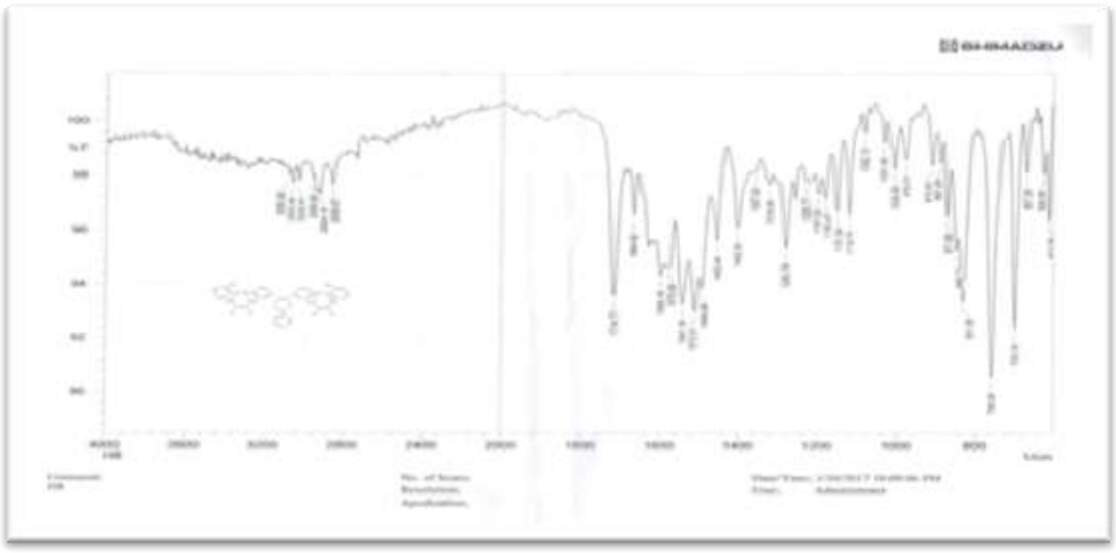


Figure 11- FT-IR- spectrum of compound (C5).

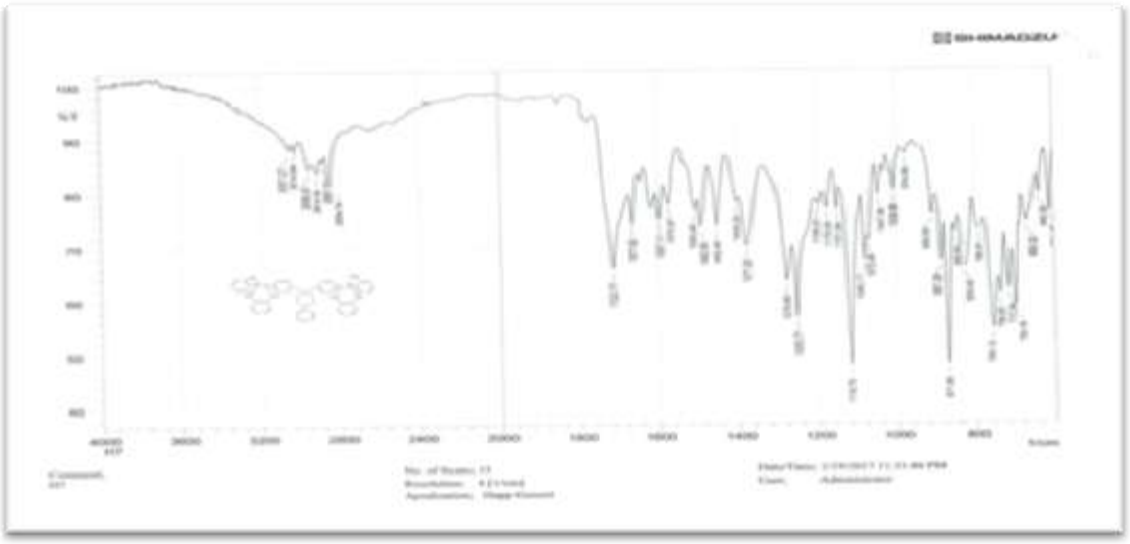


Figure 12- FT-IR- spectrum of compound (C6)

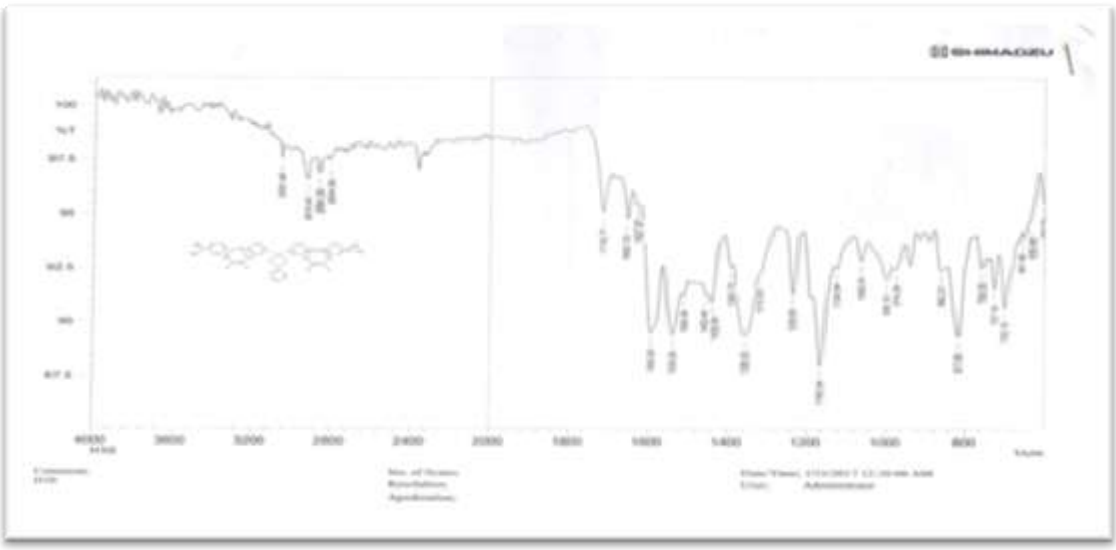


Figure 13- FT-IR spectrum of compound (C7).

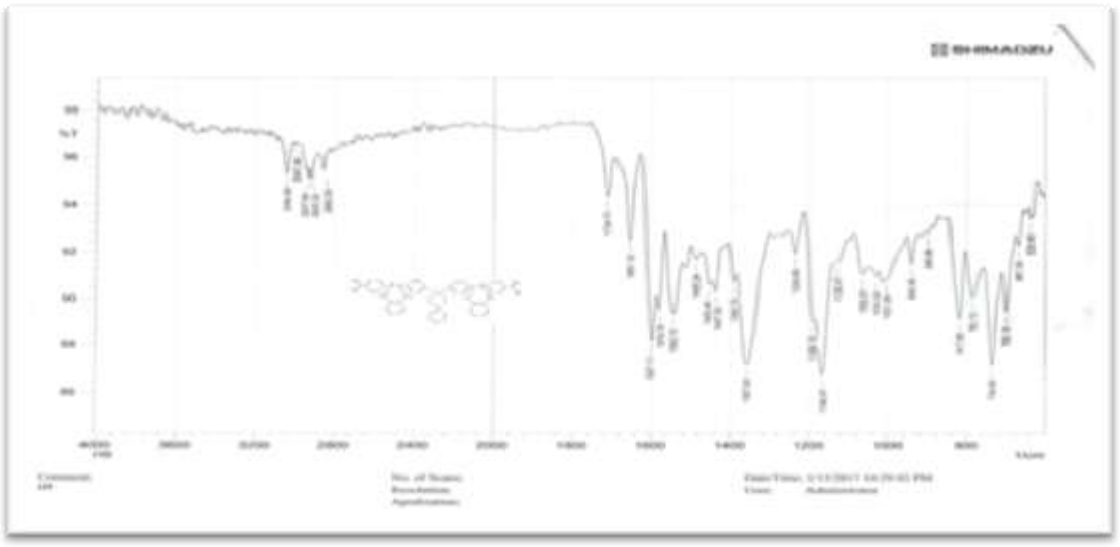


Figure 14- FT-IR spectrum of compound (C8).

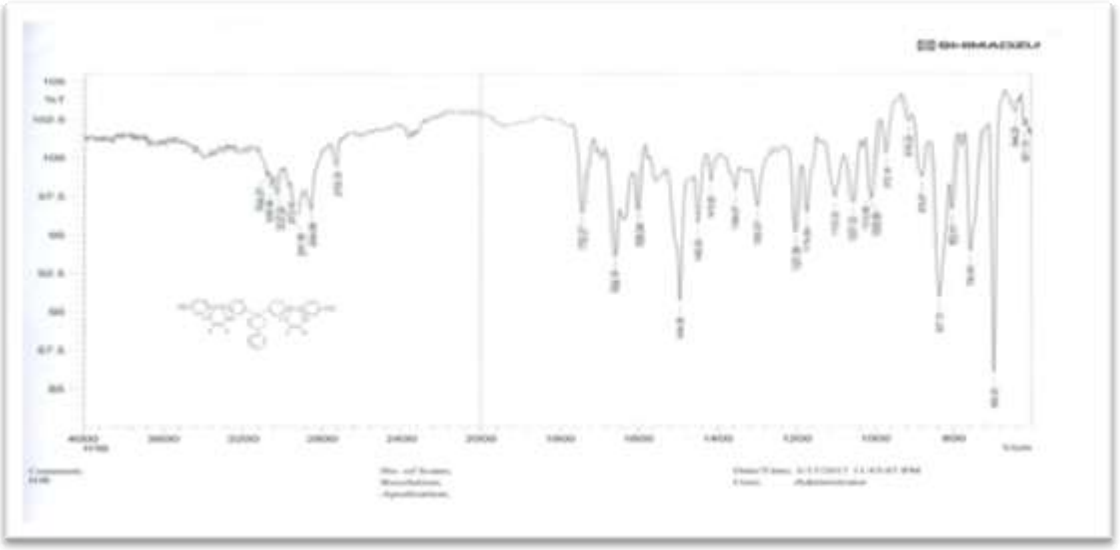


Figure 15- FT-IR spectrum of compound (C9).

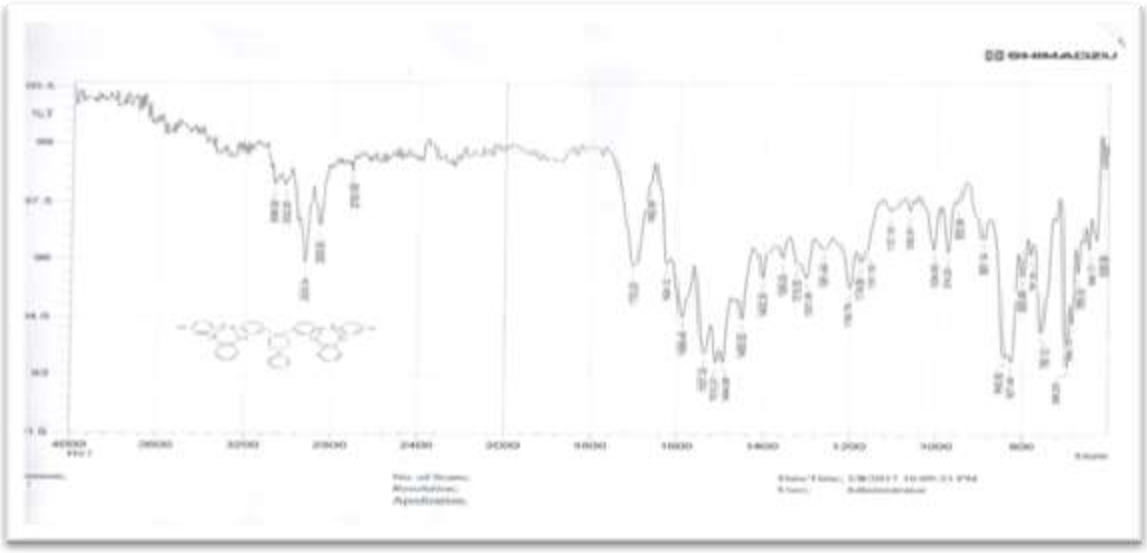


Figure 16- FT-IR spectrum of compound (C10).

Biological activity

A comparative zone of inhibition (mm) for Schiff bases, oxazipene and standard drugs are reported in Table-1. The test results presented in Table-2 from which it is clear that the prepared Schiff bases have moderate antibacterialactivity in comparison with standard drugs. Oxazipene compounds showed highly active against *E. coli* as compared to Schiff bases.

Table 2- Biological activity of the synthesized compounds**.**

Compound	**Antibacterial activity zone of inhibition (mm)**			
	E.coli	*K. pneumonia*	*S. pyogenes*	*S. aureus*
C 1	9	8	9	8
C 2	8	9	10	12
C 3	9	8	9	8
C 4	8	9	10	9
C 5	12	11	13	12
C 6	18	14	12	11
C 7	11	9	11	12
C 8	13	10	12	12
C 9	12	11	10	10
C 10	12	9	11	10
Ampicillin (std.)	22	18	20	23

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