Synthesis and characterization of some new bis 1,3-oxazepines and 1,3-imidazolidine with evaluating of its biological activity.

***Fawzi Hameed Jumaa and *Rashed Fadel Abbass.**

***Department of Chemistry,College of Education for Woman, Tikrit.**

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Abstract:

In this study some new compounds have been synthesized including preparation of some different Schiff bases (1-5) from the reaction of aromatic amines with terphthadehyde in absolute ethanol and converted into derivatives of 1,3-Oxazepine (of ring closure reaction (2 +5) of Schiff bases with maleic anhydride in benzene (6-10) besides the 1,3- Imidazolidenon (11-15) and evaluation of biological activity for some of them. The prepared compounds were characterized by FT-IR spectra and ^{1}H-NMR spectra for some of the prepared compounds besides the determination of their melting points and TLC (Thin Layer Chromatography.

تحضير وتشخيص بس 1و3- اوكسازبين وبس 1و 3 –ايميدازوليدين وتقييم فعاليتها البايولوجية.

فوزي حميد جمعة ورشيد فاضل عباس

قسم الكيمياء –كلية التربية للبنات-جامعة تكريت /العراق.

مفتاح الكلمات:قواعد شيف,اوكسازبين,اميدازوليدون

الملخص :

تم في هذا البحث تحضير بعض المركبات والمتضمنة قواعد شف مختلفة من تفاعل الامينات الاروماتية مع الترفثالديهايد بالايثانول المطلق ثم تم تحويلها الى مشتقات 1و3-اوكسازبين (من تفاعلات غلق الحلقة 2+5) لقواعد شف مع ماليك انهدريد بالبنزين (6-10) بجانب الايميدازوليدين (11-15) وتقييم الفعالية البايولوجية للبعض منها. شخصت المركبات المحضرة من خلال اطياف الاشعة تحت الحمراء واطياف الرنين النووي المغناطيسي للبروتون للبعض منها بالاضافة الى تعيين درجات الانصهار وكروماتوغرافيا الطبقة الرقيقة.

Introduction:

Heterocyclic compounds are considered an important branch of organic compounds due to their application in drugs and industrial studies [(1)]. Heterocyclic compounds have a wide range of applications, but are of particular interest in medicinal chemistry[(2)] and industrial application. The history of heterocyclic chemistry began in the (1800), in step with the development of organic chemistry.

Tetrazole It is a five membered-ring containing four nitrogen atoms with one carbon substituted tetrazoles are reported to possess antibacterial, antihypertensive, antiviral, analgesic, anti-inflammatory, anticancer activities [3,4]. A series of substituted tetrazole have been synthesized by different methods such as from pyridine with sodium azide to give 2-azido pyridine[22] (2-azido-azines)are in equilibrium with fused tetrazoles[23], the position of the equilibrium being very sensitive to substituent influence, for example for Tetrazole (1,5, α) pyridine, the equilibrium lies predominantly towards the closed form[5].

El-Gaby et. al. [6], prepared 6-methyl-7-styryl-tetrazo[1,5-b]pyridazin-8-carbonitrile[25] as a novel compound by reaction of 3-chloro-4-cyano-6-methyl-5-styrylpyridazine with sodium azide in dimethylsulphoxide. Oxazepine : It is a seven membered ring that contains two heteroatoms (Oxygen and Nitrogen). Oxazepama (serax) marketed under brand names : Alepam , Serax , Murelax , Serax-Sobril are the first drag of chemical series of compounds , 3-hydroxy benzo diazepines , comprised of two aromatic ring is fused to the seven-membered ring and it contains chloro-substituent or some other electronegative group[7] .

Oxazepam (serax) is 7-chloro-1,4-dihydro-3-hydroxy-5-phenyl-2H-1,4 benzodiazepine -2-one. S. bilgic., et a.,l[8] synthesized 2-aryl-1,2dihydronaphthol[1,2-f][1,4] oxazepine -3(4H)ones. From 2-hydroxy-1-naphthaldehyde and aniline . 2-hydroxy-1-naphthaldehyde was treated with aniline to give Schiff base which treated with sodium borohydrate then the product was reacted with chloroacetylchloride to give oxazepine derivatives.

It is also known that the presence of an azo moiety in different types of Schiff bases can lead them to exhibit pesticidal activities. Both Schiff bases and azo compounds are important structures in the medicinal and pharmaceutical fields [9] and it has been suggested that the azomethine linkage might be responsible for biological activities displayed by Schiff bases.

Imidazole, imidazolidine-2,4-dione, imidazolidine-2 thioxo-4-one and their heterocyclic derivatives represent an interesting class of compounds which possess a wide range of biological activities ,such anti-inflammatory [10], antimicrobial[11],(antifungal,antibacterial and anticonvulsant[12]activities. Most of the work have been carried out substitution at the 3 and 5 position of the imidazolidine derivatives and investigated and the antimicrobial activity[13,14].

Experimental:

1-Melting points were recorded with Stuart Melting point apparatus and were uncorrected.

2-Infra red spectra (FT-IR) were recorded on Shimadzu FT-IR-8300 spectrophotometer in Ibn Sina State Company (ISSC).

3-^{1}H-NMR spectra were recorded on a BRUKER-400 MHz operating at 300 MHZ with tetra methyl silane as internal standard in $CDCl_3$ and DMSO-d_6 as a solvent, measurements were made at Chemistry Department, AL-Bait University-Jordin.

4-Thin layer Chromatography (TLC) was carried out by using alumina plates percolated with silica–gel, supplied by Merck. Spots were detected with iodine vapor.

5-The biological activity was performed by Biology Department College of Science, University of Tikrit.

1-Preparation of Schiff Bases (1-5) [15]

A solution of (0.02mol) of aromatic amines or its derivatives in (40ml)ethanol was added to (0.01mol) of terephthaldehyde in (20ml) ethanol then the mixture was refluxed for (3hr.). the mixture was cooled to room temperature, filtered and re-crystallized ,Table (1).

2-Preparation of 4,4-bis- (substituted-phenylene 2,3-dihydro-1,3-oxazepine-4,7-dione)phenylene (6-10).

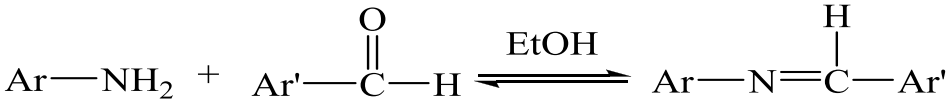
A mixture of Schiff base [1-5] (0.01 mole) and (0.02) mole of maleic or phthaleic anhydride in (20 ml) of benzene was refluxed for (24) hours then the solvent evaporated and then the formed precipitate was re crystallized from appropriate solvents , yield (65%).

3-preparation of imidazolidinone derivatives (11-15).

A mixture of Schiff base (0.01mole) and Tryptofan (0.02mole) in (20 ml) of THF was refluxed for (24) hours then it cold to room temperature and the formed precipitate was filtered and re crystallized from ethanol , yield (75%).

Results and Discussion:

The Schiff bases were prepare by the reaction of amines (2mole) with (1mole)of terephthaldehyde in absolute ethanol:



Ar = 4-Br , 4- NO_2 ,H , 4-CH_3 ,4-CH_3O , $Ar^- = C_7H_6O$

The prepared compounds were characterized by FT-IR spectra ,H-NMR spectra and the melting points were recorded and checked by TLC.

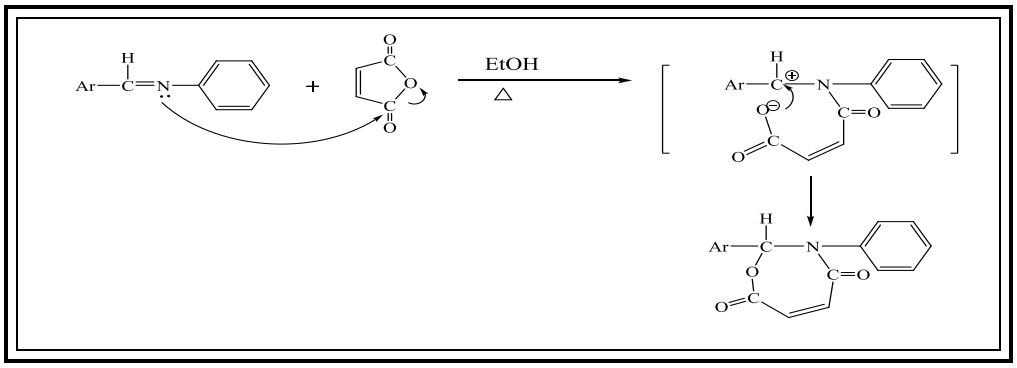
The FT-IR spectrum of Schiff bases showed the appearance of bands at 3250 cm^{-1} due to amino group. The new band which appears at (1625 -1577)cm^{-1} in the IR spectrum of (3) which is attributed to the new azomethine (C=N) group. Besides the appearance of bands at (1475-1456)$cm^{-1}$and at (1581-1570)cm^{-1} due to (C=C) aromatic and at (3103-3047)cm^{-1} attributed to (C-H)aromatic Table (4).fig.(2).

^{1}H-NMR spectrum for compound (1), showed single peak at (3.34) ppm due to(N=C-H) proton of imine group besides the peak at (2.5)ppm due to protons of DMSO and peaks at (7.6-7.2) ppm attributed to aromatic protons.fig.(3).

^{1}H-NMR spectrum for compound (3), showed single peak at (3.36) ppm due to(N=C-H) proton of imine group besides the peak at (2.5)ppm due to protons of DMSO and peaks at (7.4-7.2) ppm attributed to aromatic protons.fig.(4).

^{1}H-NMR spectrum for compound (4), showed single peak at (3.34) ppm due to(N=C-H) proton of imine group besides the peak at (2.5)ppm due to protons of DMSO and peaks at (8-7.2) ppm attributed to aromatic protons and peak at (2.3)ppm due to (CH_3). fig.(5).

Oxazepines compounds (6-10) were prepared from the reaction of maleic or phthalic anhydride with Schiff bases (1-5) in benzene.

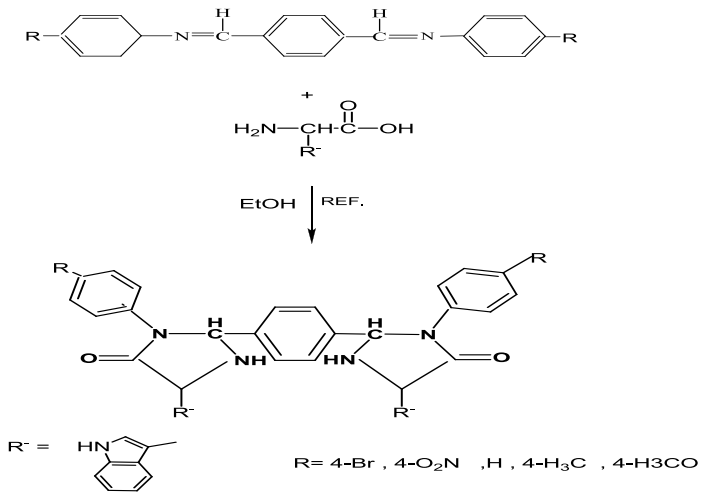


The FT-IR spectrum showed the bands at (1192-1110) cm^{-1} due to (C-N) and at (1708-1699)cm^{-1}, at (1668-1664) cm^{-1}due to (C=O) for lacton ,lactam compounds respectively besides other two bands at (1496-1472) cm^{-1} and at (1600-1508) cm^{-1} due to (C=C) aromatic and appearance of band at (1286-1265) cm^{-1}due to (C-O) ,table(5).figs6,7 compound (6,7) .

^{1}H-NMR spectrum for compound (6), showed single peak at (3.3) ppm due to methyl protons besides the peak at (2.5)ppm due to protons of DMSO and peaks at (6.3-6.4) ppm attributed to olephenic protons and peak at (7.6-7.2)ppm due to aromatic protons and a single peak at (4.4)ppm due to (OH) proton. fig.(8).

^{1}H-NMR spectrum for compound (8), showed single peak at (4.3-4.2) ppm due to methyl protons besides the peak at (2.5)ppm due to protons of DMSO and peaks at (6.4-6.2) ppm attributed to olephenic protons and peak at (7.5-7.1)ppm due to aromatic protons. figs.(9,10).

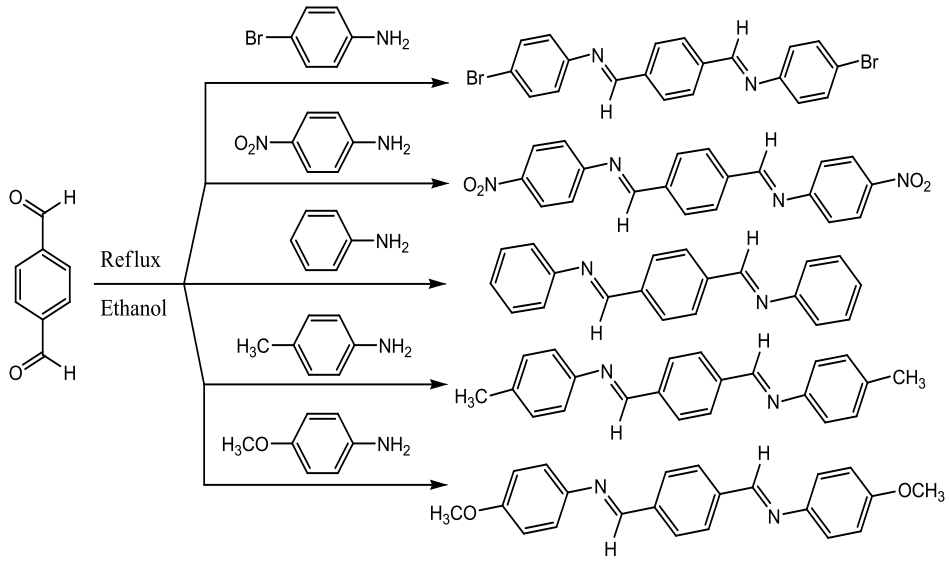
Imidazolidins compounds (11-15) were prepared from the reaction of tryptophan (amino acid) with Schiff bases.

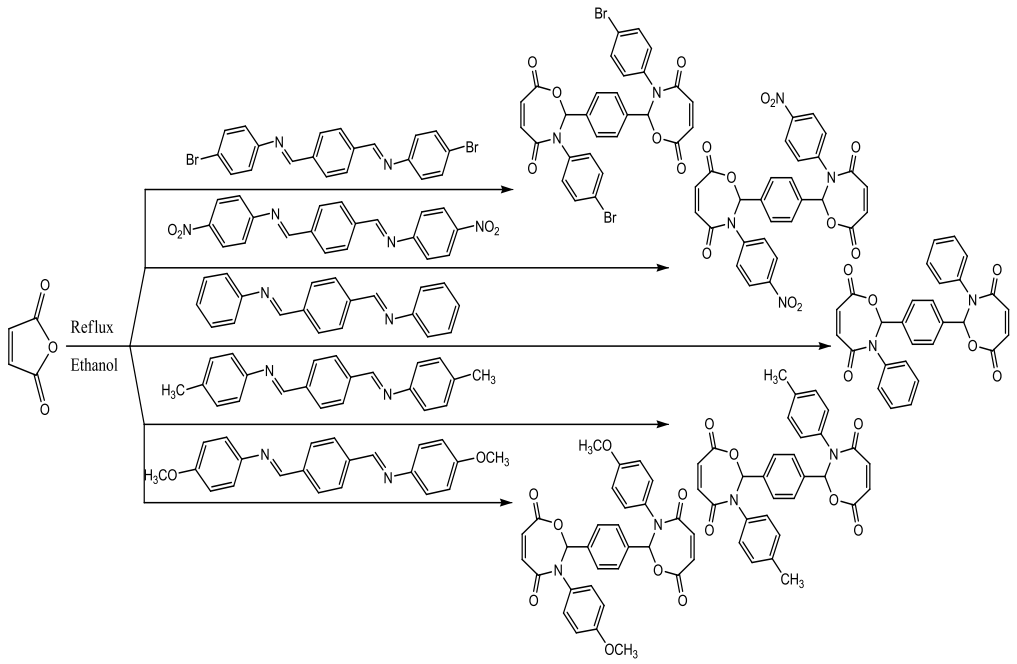


The prepared compounds were characterized by FT-IR spectra and H-NMR spectra. The FT-IR spectra showed the bands at (1172-1161) cm^{-1} due to (C-N) and at (1674-1666)cm^{-1} due to (C=O) and at (3082-3040) cm^{-1}due to (C=C) Aromatic and at (3424-3412) cm^{-1} due to (N-H). table (6),figs. (11,12) for compounds(11,15).

^{1}H-NMR spectrum for compound (11), showed single peak at (3.4) ppm due to methyl protons besides the peak at (2.5)ppm due to protons of DMSO and peaks at (7.9-6.02) ppm attributed to aromatic protons and peaks at (6.3-6.0)ppm due to para substituted protons with a single peak at (10.0)ppm due to (N-H). figs.(13,14).

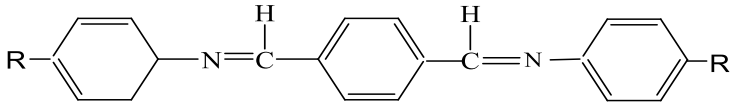
Scheme 1: represents Schiff bases compounds(1-5).





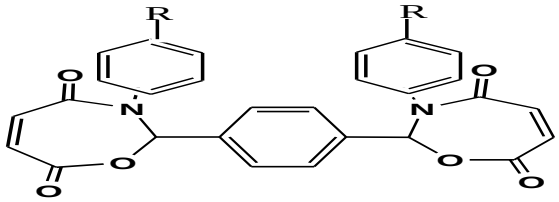
Scheme 2: represents oxazepines compounds(6-10).

Table (1): physical properties of Schiff bases (1-5).



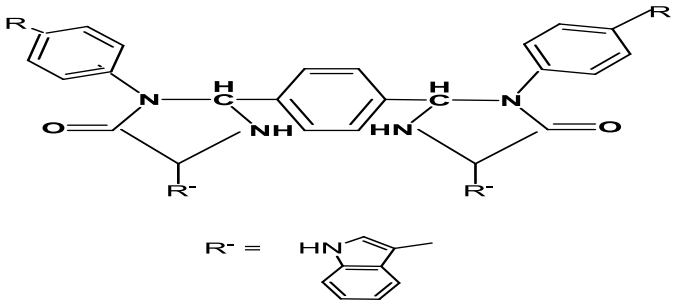
Comp. No.	R	Molecular formula	Colour	M.P(^{0}C)	Yield (%)
1	4-Br	$C_{20}H_{14}N_2Br_2$	yellow	207-210	81
2	4- NO_2	$C_{20}H_{14}N_4O_4$	deep yellow	274-276	82
3	H	$C_{20}H_{16}N_2$	Yellow	163-165	86
4	4-CH_3	$C_{22}H_{20}N_2$	yellow	187-189	75
5	4-OCH_3	$C_{22}H_{20}N_2O_2$	yellow	82-84	80

Table (2): physical properties of Schiff bases (6-10).



Comp. No.	R	Molecular formula	Colour	M.P(^{0}C)	Yield (%)
6	4-Br	$C_{28}H_{18}N_2O_6Br$	Yellow	207-210	80
7	4-NO_2	$C_{28}H_{18}N_4O_{10}$	Pale yellow	190-192	86
8	H	$C_{28}H_{19}N_2O_6$	Pale yellow	167-169	81
9	4-CH_3	$C_{30}H_{24}N_2O_6$	yellow	213-215	88
10	4-OCH_3	$C_{30}H_{24}N_2O_8$	Pale yellow	198-200	85

Table (3): physical properties of Imidazolidenes(11-15).



Comp. No.	R	Molecular formula	Colour	M.P(^{0}C)	Yield (%)
11	4-Br	$C_{42}H_{32}N_6O_2Br_2$	Yellow	176-178	49
12	4-NO_2	$C_{42}H_{32}N_8O_6$	orange	190-192	76
13	H	$C_{42}H_{34}N_6O_2$	yellow	170-172	79
14	4-CH_3	$C_{44}H_{40}N_6O_2$	yellow	156-158	91
15	4-OCH_3	$C_{44}H_{40}N_6O_4$	yellow	238-240	89

Table(4): FT-IR spectrum data for Schiff bases(1-5).

Comp. No.	R	ν C=N	ν C-C	ν (C-H) Ar	ν (C=C) Ar	ν C-N	Others
1	4-Br	1625	1278	3090	1475,1581	1180	ν(Br-C), 804
2	4-NO_2	1618	1286	3103	1556 1581	1168	ν(NO_2), asy.1516, sym.1334
3	H	1608	1292	3047	1460, 1585	1172	δ $(C-H)_{Ar}$ 780, 860
4	4-CH_3	1600	1311	3055	1481, 1580	1164	ν(CH_3), asy.2974,sym.2870
5	4-OCH_3	1577	1280	3066	1460 ,1570	1176	OCH_3,1180

Table(5): FT-IR spectrum data for oxazepines(6--10).

Comp. No.	R	νC-O	νC=O Lacton Lactam	νC-H	ν(C-H) Ar	ν(C=C)Ar	νC-N	Others
6	4-Br	1272	1708 1664	2925	3040	1475 1600	1116	ν(Br-C), 804
7	4-NO_2	1286	1704 1668	2933	3039	1472 1598	1110	ν(NO_2),asy. 1516, sym.1304
8	H	1280	1703 1665	2960	3035	1477 1598	1134	ν(C-H), 2870
9	4-CH_3	1265	1699	2921	3097	1492 1596	1166	δ(CH_3),asy. 1446, sym.1369
10	4-OCH_3	1270	1699 1668	2956	3091	1496 1508	1192	ν (OCH_3), 1111

Table(6): FT-IR spectrum data for Imidazolidenes(11-15).

Comp. No.	R	νNH	νC-C	νC=O	ν(C-H) Ar	$\nu(C=C)_{Ar}$	νC-N	Others
11	4-Br	3424	1280	1647	3040	1473 1560	1161	ν(C-Br), 850
12	4-NO_2	3387	1276	1674	3066	1442 1573	1164	ν(NO_2), asy.1346, sym.1512
13	H	3285	1271	1672	3066	1480 1560	1170	-
14	CH_3	3290	1265	1666	3082	1460 1539	1164	ð (CH_3),asy. 1361, sym.1460
15	4-OCH_3	3412	1265	1670	3060	1419 1555	1172	4-OCH_3(1112)

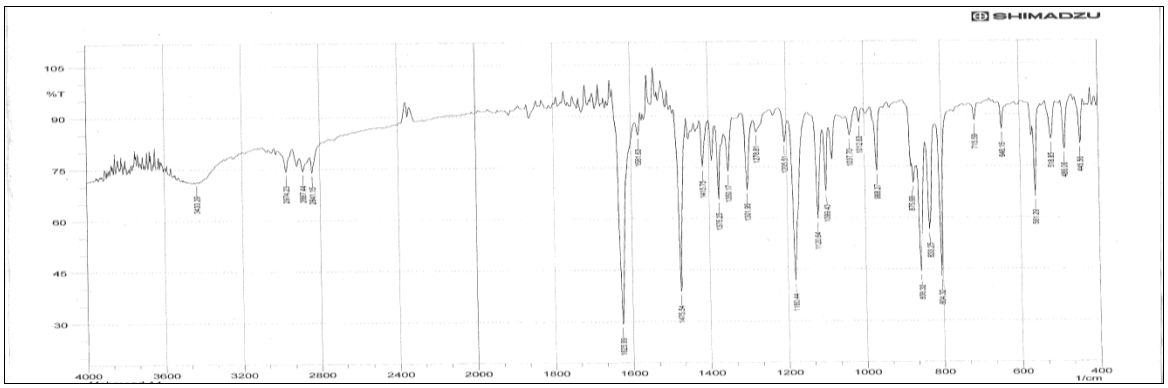


Fig.(1):FT-IR spectrum of compound(1).

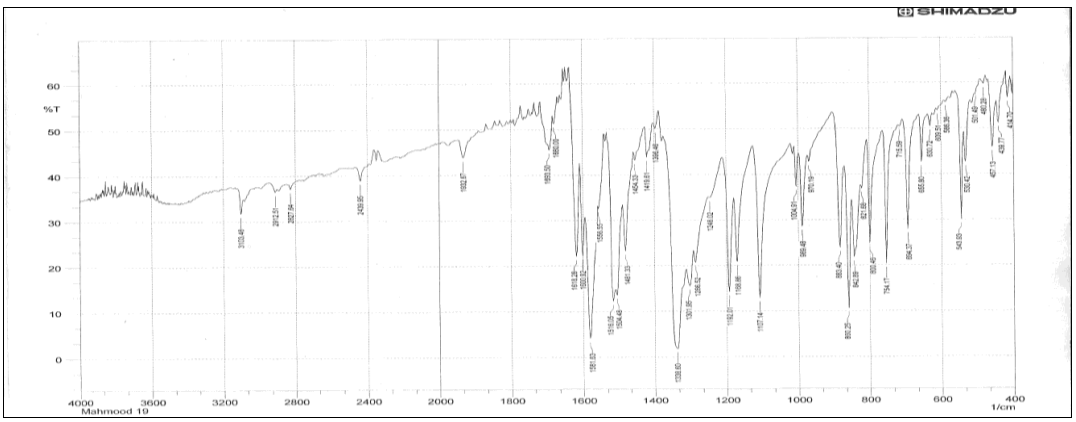


Fig.(2):FT-IR spectrum of compound(2).

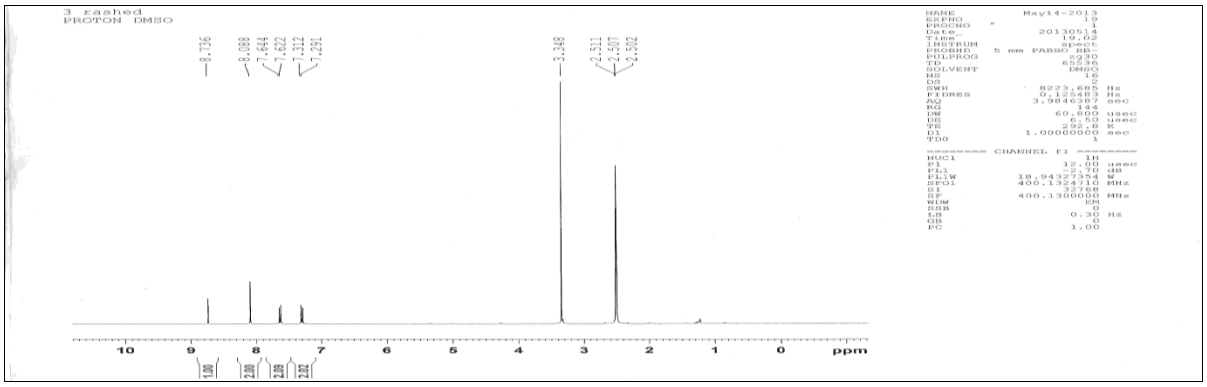


Fig.(3):H-NMR spectrum of compound(1).

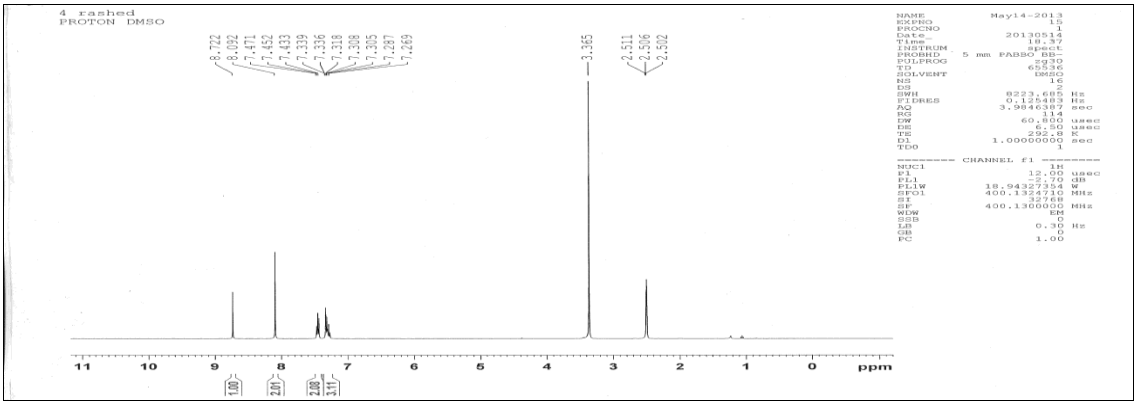


Fig.(4):H-NMR spectrum of compound(3).

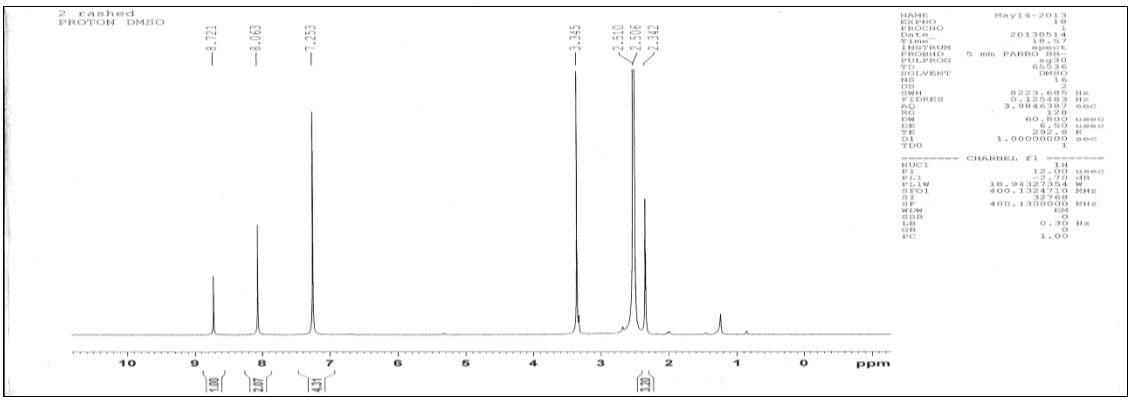


Fig.(5):H-NMR spectrum of compound(4).

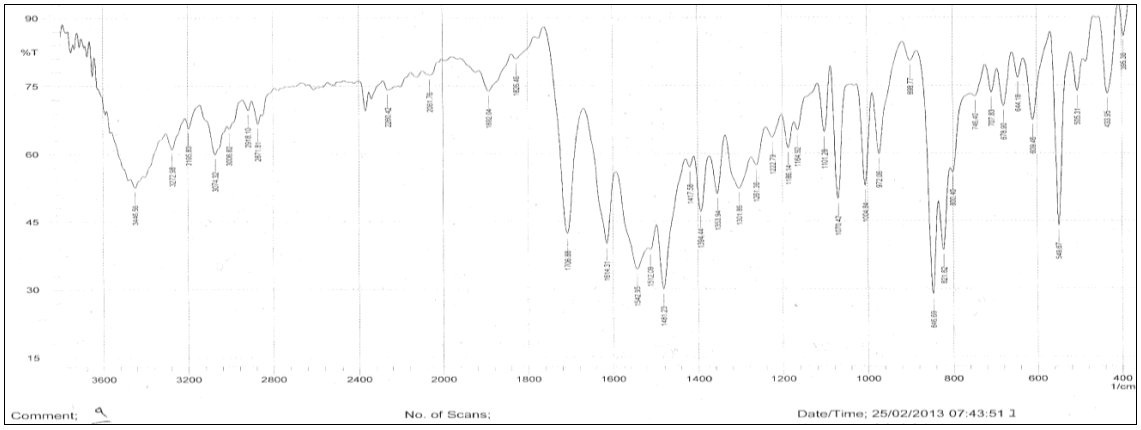


Fig.(6):FT-IR spectrum of compound(6).

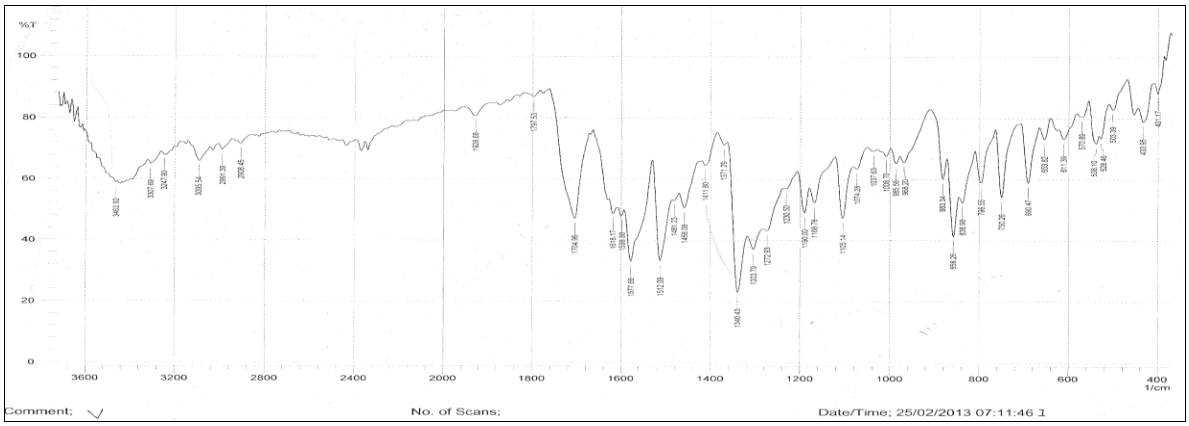


Fig.(7):FT-IR spectrum of compound(7).

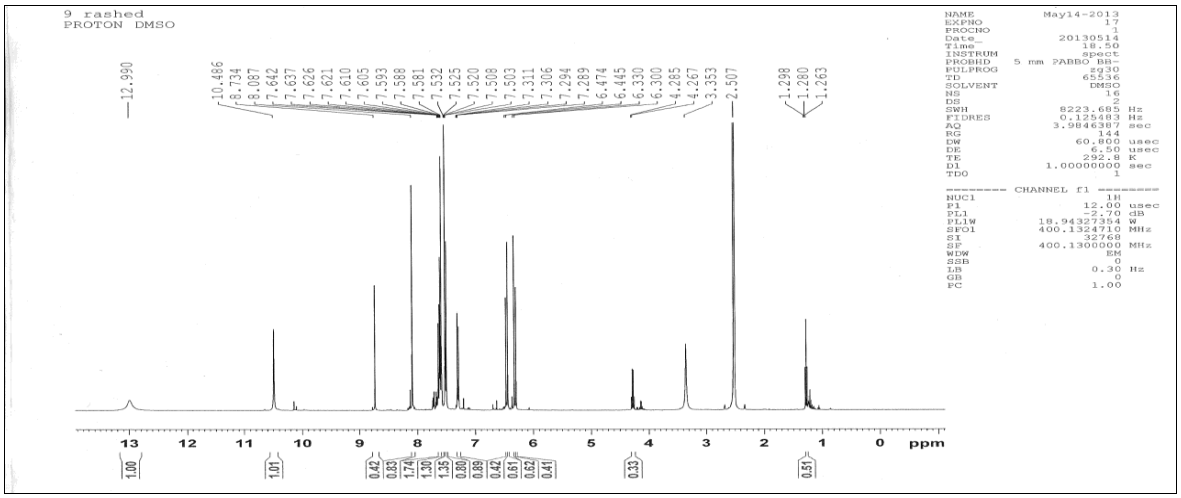


Fig.(8):H-NMR spectrum of compound(6).

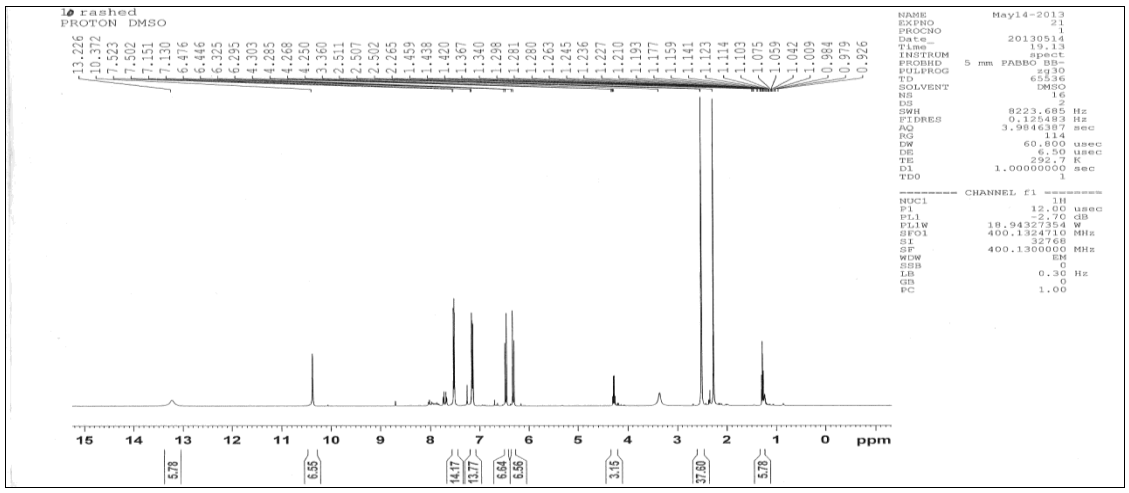


Fig.(9):H-NMR spectrum of compound(8).

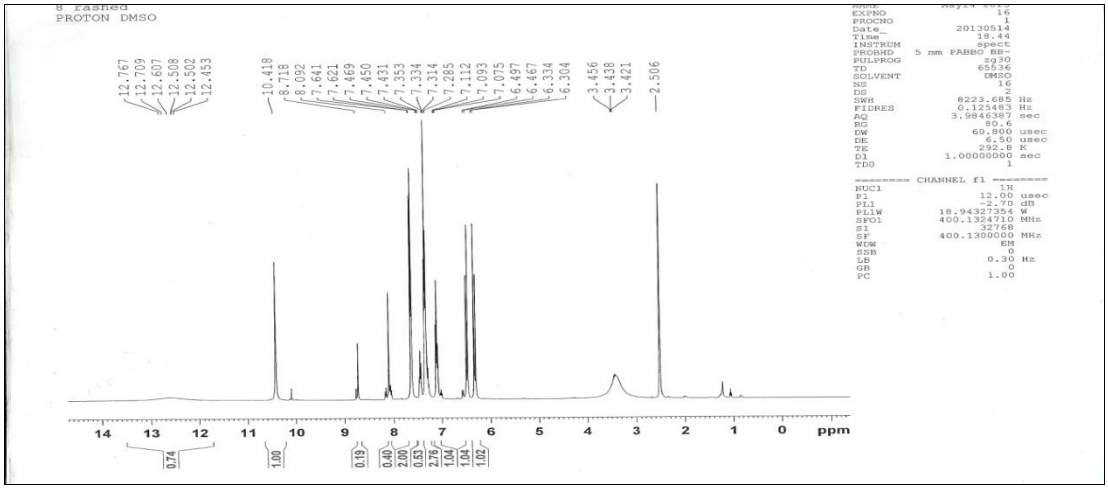


Fig.(10):H-NMR spectrum of compound(9).

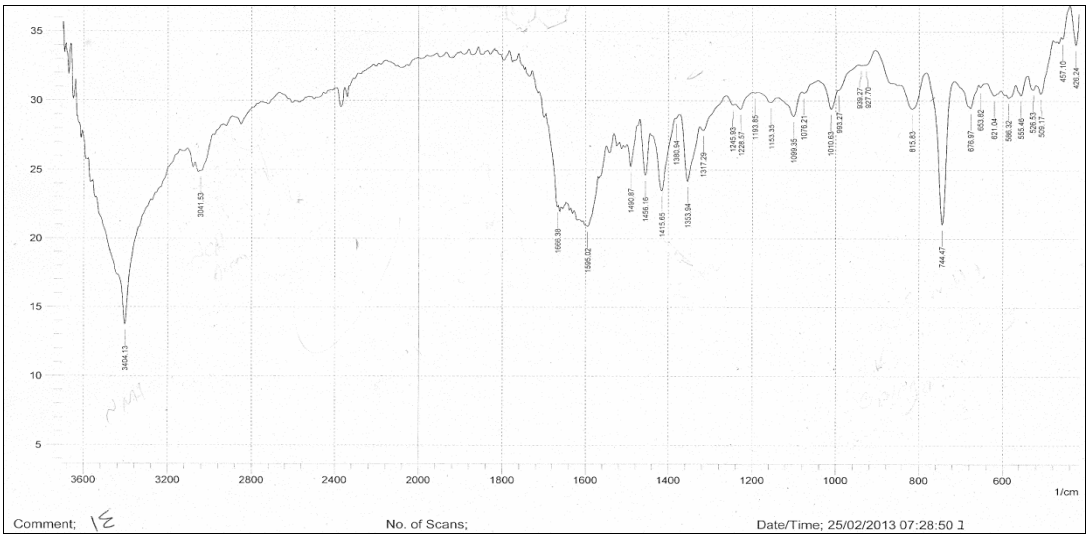


Fig.(11):FT-IR spectrum of compound(11).

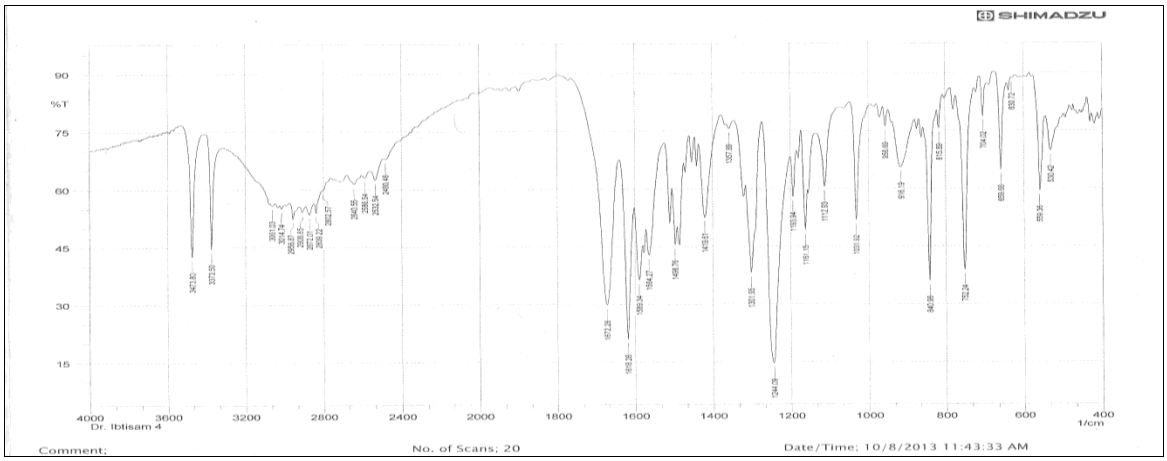


Fig.(12):FT-IR spectrum of compound(15).

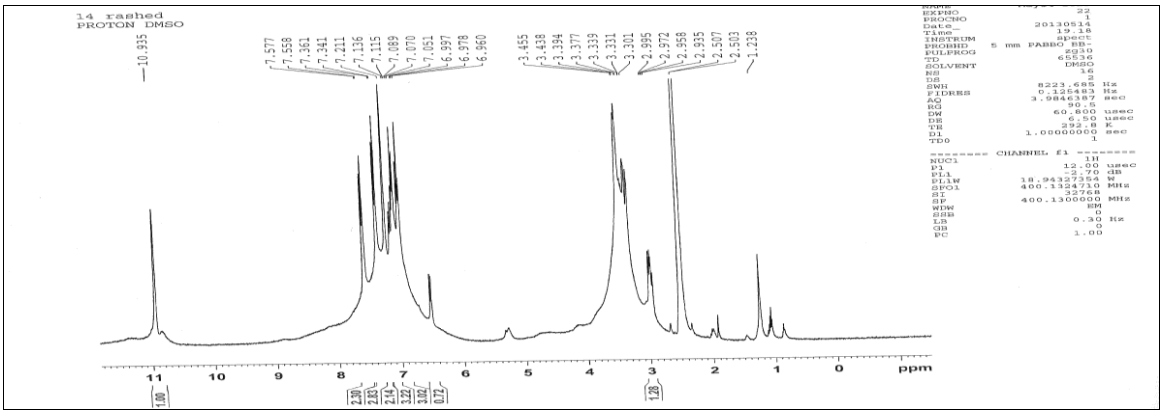


Fig.(13):H-NMR spectrum of compound(11).

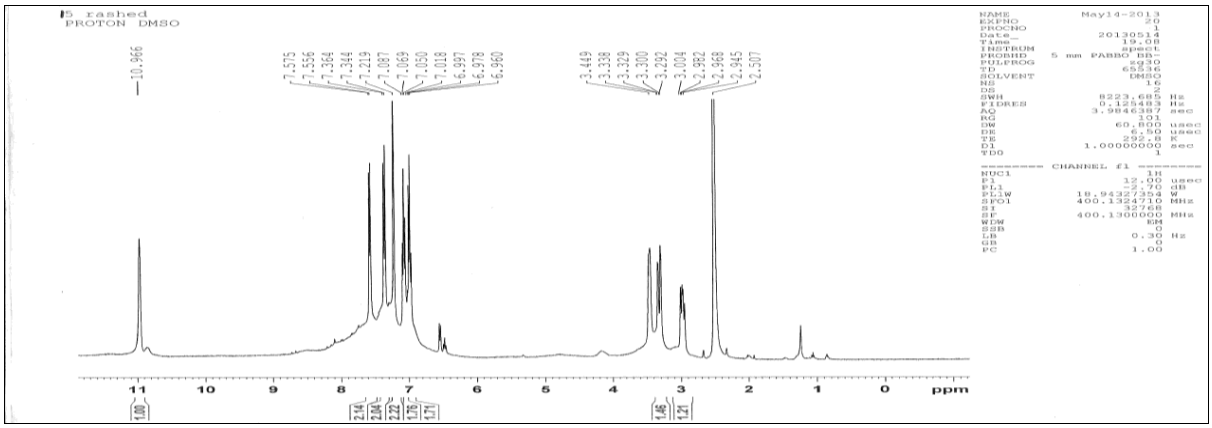


Fig.(14):H-NMR spectrum of compound(13).

Biological Activity:

Here in this work, the sensitivity test was performed according to the Kerby –Bauer method[ ]. Compound (8) was assayed for its antimicrobial activity in vitro against Gram-negative bacteria (*Escherichia coli*) and Gram-positive bacteria (*staphylococcus aurous*). Prepared agar and Petri dishes were sterilized by autoclaving for 15min at 121C°. DMSO was used as a solvent. These plates were incubated at 37C° for 24h for both bacteria. The inhibition zones caused by the various compounds were examined. The results of the preliminary screening tests are listed in table (8).

The biological activity test showed that compounds with free (-SH) groups and free ($-NH_2$) groups having a biological effect on each of *E.Coli* and *Staph.aureus*, these compounds are also considered biologically active on *bacteria* .

Table (7): inhibition zooms for prepared compounds (1-15).

Comp.No.	*Ps. aeruginosa*	*St. aureus*
1	-+	-
2	-	-+
3	+	+
4	+	-+
5	-	+
6	++	-
7	+	-+
8	++	+
9	+	-+
10	++	-+
11	+	+
12	-	-
13	+	+
14	++	-
15	+	+

inhibition =* (-) *(5-10) mm =* (+) , *(11-20) mm = ++ , more than (20)mm =+

References:.

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