Synthesis, Characterization and Study of Biological Activity of Some New Schiff Bases ,1,3-Oxazepine and Tetrazole Derived from 2,2 di thiophenyl Acetic Acid

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Abstract

In this study new derivatives of Schiff bases 5-8 , 1,3- oxazepine 9-16 and tetrazoles 17-19 have been synthesized from the new starting material 1 which has synthesized the reaction of one mole of dichloro acetic acid and two moles of thiophenol , the esters 2-3 were synthesized from the reaction of compound 1 with methanol or ethanol respectively in the presence of H_2SO_4 as catalyst then 2,2-dithiophenylaceto Hydrazide 4 were synthesized from the reaction of 2 or 3 with hydrazine hydrate 80 % , Schiff bases 5-8 were synthesized from the reaction of 4 with appropriate aldehyde or ketone .Treatment of Schiff bases with maleic and phathalic anhydride in dry benzene to give 1,3-oxazepen derivatives 9-16 and with sodium azide in tetrahydrofuran (THF) afforded tetrazole derivatives 17-19. All these compounds have been characterized from their melting pointes, FTIR, ^{1}HNMR and compounds 1,5 and 18 by mass spectrometry. Derivatives 6,7,11,16,17 and 18 were tested against inhibition of *E. coli* and. *Staphylococcus- aureus* and were all funds to be active. Scheme (1).

Keyword: Dithiophenyl, Schiff bases, 1,3-oxazepien, tetrazole.

Introduction

Heterocyclic compounds are very wide spread in the natural and in non-natural molecules, from this are the compounds which entered as an essential compound in the life, many compounds such as vitamins, essential amino acids, hormones and the synthetic drugs includes heterocyclic ring system, also they are very important in the pharmacological and synthetic fields [1].

Schiff bases are compounds have an azomethine group (-C=N-), They have important application in pharmaceutical fields and in polymer chemistry in addition of their biological activity such as antibacterial, antifungal, anticancer and another application [2]

1,3-Oxazepines have significant application in medicine and in the bioactivity such as hypnotic muscle relaxation, antagonistic, anti-inflammatory, antifungal and another uses [3] also they have been used as protective of amino group in the organic synthesis [4].

Tetrazole has five member hetroaromatic ring [5]. it is an important ring have many applications in the medicine chemistry and in materials application [6]. In this work we intend to synthesize new heterocyclic compounds including tetrazole and 1,3-oxazepein derivatives beginning from the synthesis of new 2,2-dithiophenyl acetic acid starting material derived from dichloro acetic acid.

Experimental

Instrument

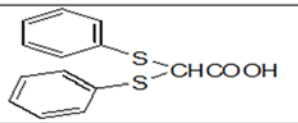
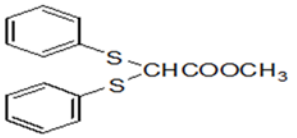
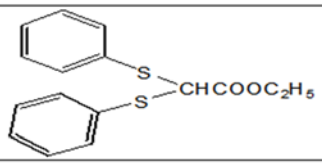
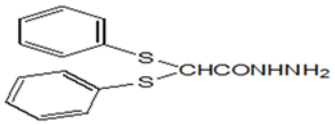
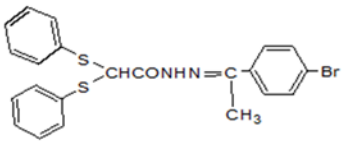
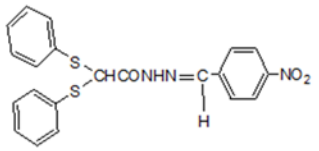
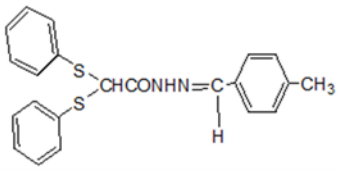
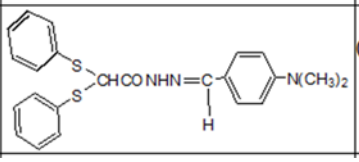
Melting points were recorded on Gallenkamp melting device and were uncorrected , FTIR spectra were recorded on Shimadzu FTIR 8400 fourier transform infrared spectrophotometer using KBr disc , ^{1}HNMR spectra were recorded on Bruker 400 MhZ spectrometer using DMSO-d_6 as a solvent and tetra methyl silane (TMS) as internal standard , mass spectra were recorded on Gcms QP Gas chromatography mass spectrometer agilent technology (HP) .

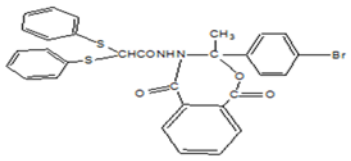
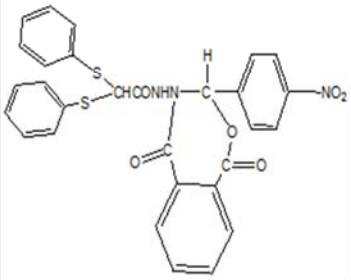
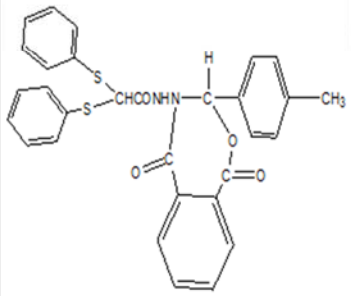
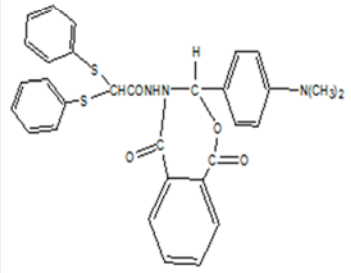
Chemicals All the chemical reagent was used as a received, and were not purification.

-Synthesis of 2,2-dithiophenyl acetic acid [7] 1:

Thiophenol (1.7 g ,0.015 mole) was dissolved in aqueous solution of 50 ml distilled water contain a potassium hydroxide (1.1 g ,0.02 mole); then carefully dichloro acetic acid (1g ,0.007 mole) was added. The mixture of reaction was heated on the sand bath for 6 hrs. After completion, the mixture cooled to room temperature and acidified by hydrochloric acid 10 % to precipitate the acetic acid derivative, then the crude product was recrystallized from ethanol to give high yield (80 %) with melting point (60 ^{0}C), The physical properties of this compound are shown in the table (1)

Table (1): physical properties of compounds [1-19]

Comp No.	Compound Structure	Nomenclature	Molecular Formula	M.W g/ mol	M.P. ^{0}C	Yield %	color	Solvent recryst
1		2,2-dithiophenyl acetic acid	$C_{14}H_{12}O_2S_2$	276	70	60	Pale yellow	Ethanol
2		methyl 2,2-dithiophenyl acetate	$C_{15}H_{14}O_2S_2$	290	gummy	93	Yellow	Ethanol -
3		ethyl 2,2-dithiophenyl acetate	$C_{16}H_{16}O_2S_2$	306	gummy	95	red	Ethanol
4		2,2- dithiophenyl aceto hydrazide	$C_{14}H_{14}N_2OS_2$	290	50	90	White Brownish	Ethanol
5		N'-(1-(4-bromophenyl) ethylidene)-2,2-dithiophenyl acetohydrazide	$C_{22}H_{19}BrN_2OS_2$	471	159	80	yellow	Ethanol
6		N'-(4-nitrobenzylidene)-2,2- dithiophenyl acetohydrazide	$C_{21}H_{17}N_3O_3S_2$	423	290	76	yellow	Acetone
7		N'-(4-methylbenzylidene)-2,2-dithiophenyl acetohydrazide	$C_{22}H_{20}N_2OS_2$	392	120	75	yellow	Methanol
8		N'-(4-(dimethylamino)benzylidene)-2,2-dithiophenyl acetohydrazide	$C_{23}H_{23}N_3OS_2$	421	150	60	red	Ethanol

9		N-(3-(4-bromophenyl)-3-methyl-1,5-dioxobenzo[e][1,3]oxazepin-4(1H,3H,5H)-yl)-2,2-dithiophenyl acetamide	$C_{30}H_{23}BrN_2O_4S_2$	618	140	67	green	Ethanol
10		N-(3-(4-nitrophenyl)-1,5-dioxobenzo[e][1,3]oxazepin-4(1H,3H,5H)-yl)-2,2-dithiophenyl acetamide	$C_{29}H_{21}N_3O_6S_2$	571	270	76	Orange	Ethanol
11		N-(1,5-dioxo-3-p-tolylbenzo[e][1,3]oxazepin-4(1H,3H,5H)-yl)-2,2-dithiophenyl acetamide	$C_{30}H_{24}N_2O_4S_2$	540	110	75	Pall Green	Methanol
12		N-(3-(4-(dimethylamino)phenyl)-1,5-dioxobenzo[e][1,3]oxazepin-4(1H,3H,5H)-yl)-2,2-dithiophenyl acetamide	$C_{31}H_{27}N_3O_4S_2$	569	180	60	Deep red	Methanol

- **Synthesis of alkyl 2,2-dithiophenyl acetat [8] 2-3:**

2, 2-dithiophenyl acetic acid 1 (1 g, 0.003 mole) was dissolved in ethanol or methanol (50 ml) then (1ml) of concentration sulfuric acid was added to the mixture. The mixture then refluxed for (6 hrs) and monitored by (TLC). When the reaction was completed it was cooled to room temperature and neutralized by ($NaHCO_3$) .The solvent was removed under reduced pressure and the crud product was diluted with water (20 ml) and extracted three times with ethyl acetate (3×40 ml). The combined organic layers were dried over magnesium sulphate and the solvent was removed under reduced pressure to afford 2 and 3 as a syrup. The nomenclature, physical properties and yield of the compounds were shown in table (1)

- **Synthesis of 2,2-dithiophenylaceto Hydrazide [9] 4:**

Compound 3 (1 g, 0.0032 mole) or 4 (1g, 0.0034 mole) was dissolved in (20 ml) ethanol, then (4 ml) of hydrazine hydrate 80% was added. The reaction mixture was refluxed for (20 hrs). The precipitate which separated on cooling was filtered and recrystallized from ethanol.

- **Syntheses of N'-(Substituted) methylene)-2,2-dithiophenylacetohydrazide [10] 5-8:**

A mixture of compound 4 (1g, 0.0032 mole) was dissolved in (40 ml) of absolute ethanol. Appropriate aldehyde or ketone (0.0032 mole) was added gradually, 2-3 drops of glacial acetic acid were added. The reaction mixture was refluxed for (7-8 hrs). After completion of the reaction, ((monitored by TLC) it was cooled to room temperature, the precipitated was separated by filtration and recrystallized from appropriated solvent.

- **Syntheses of substituted 1,3 oxazepine [11] 9-16:**

Compounds 5-8 (0.0006 mole) were dissolved in dry benzene (40 ml). Subsequently (0.0006 mole) of maleic anhydride or phathalic anhydride was added, then the reaction mixture was refluxed for (6-7) hrs. The reaction mixture was cooled to room temperature. The product was filtrated and recrystallized from appropriate solvent,

- **Synthesis of N-(5-Substituted) (-2,5-dihydro-*1H*-tetrazol-1-yl)-2,2-dithiophenylacetamide [12] 17-19:**

A mixture of compounds 5-8, (0.0006 mole) and sodium azide (0.039g ,0.0006 mole) in the (THF) (15 ml) was stirred under refluxed for (4 hrs) and monitored by (TLC). Then the reaction mixture was cooled to room temperature and filtrated. The filtrate was poured in to ice- water (20 ml). the precipitate was collected and recrystallized from appropriated solvent.

Result and Discussion

Compound 1 was synthesized from the reaction of two moles of potassium benzenethiolate salt with dichloride acetic acid under reflux as we show in scheme (1). FTIR spectrum of compound 1 showed appearance of two important bands at (3057-2565) cm^{-1} due to (O-H) group [13] and at (1701) cm^{-1} due to (C=O) group [14] which they indicated formation of this compound another FTIR bands are listed in the table (3). The mass spectrum of compound 1 figure (1) indicated the exact mass of this compound at m/z = 276.

Compounds 2-3 were synthesized from the reaction of compound 1 with methanol or ethanol respectively in the presence of Sulfuric acid as catalyst. The FTIR spectra of these compounds showed clear bands at (1732-1734) cm^{-1} due to (C=O) group of ester [15] and at the range (1253-1276) cm^{-1} for (C-O) with disappearance of two bands at (3057-2565) cm^{-1} due toν (O-H) group and at (1701) cm^{-1} due to (C=O) group of acid.

Hydrazide derivative 4 was synthesized from the reaction of compounds 2 or 3 with hydrazine hydrate 80% under reflux . The FTIR spectrum of 4 showed absorption bands at 3423 cm^{-1} and 3309 cm^{-1} due to asymmetric and symmetric stretching vibration of the ($NH-NH_2$) group[16] and at (1623-1666) cm^{-1} due to (C=O) amide [17] and disappearance of two bands at (1734) cm^{-1} and at 1253-1276 cm^{-1} due to (C=O) and (C-O-C) respectively .

Compounds 5-8 were synthesized from the reaction of compound 4 with different aromatic aldehyde and ketone by using glacial acetic acid as catalyst, the FTIR spectra of these compounds showed the disappearance of two absorption bands (3423) cm^{-1} and (3309) cm^{-1} of the ($NHNH_2$) group and appearance of new band at range between (3188 - 3115) due to NH group . Also the FTIR spectra showed another absorption bands at (1668-1627) cm^{-1}, (1608-1593) cm^{-1}, (1579-1443) cm^{-1} and at (1226-1203) cm^{-1} duo to (C=O) of amide, (C=N) of imine [18] , (C=C) of aromatic rings and (C-N) of amide respectively, all main absorbing bands of the FTIR spectra of compounds 5-8 were listed in the Table (3) . The FTIR absorption bands of

compound 7 was shown in the figure (2). Mass spectrum of compound 5 figure (3) displayed the exact molecular ion.

^{1}HNMR spectrum of compound 6 figure (4) is shown δ 3.3 ppm (1,s, CHCO), δ 8.9 ppm (1,s, NH) , (7.2-8.2) ppm (15,m, aromatic and imine proton).

^{1}HNMR spectrum of compound 7 figure (5) is shown δ 3.9 ppm (1,s, CHCO) proton, δ 2.3 ppm (3,s,CH3) protons, δ 8.67ppm (1,s, NH), δ (7.3-7.78) ppm (15,m, aromatic and imine proton) .

^{1}HNMR spectrum of compound 8 figure (6) is shown δ 4.1 ppm (1,S, CHCO) proton, δ 2.9ppm (6,s,$N(CH_3)_2$) protons, δ 11.8 ppm (1,s, NH), δ (6.62-8.06) ppm (15,m, aromatic and imine proton) **.**

Compounds 9-16 were synthesized from the reaction of compounds 5-8 with phathalic and malic anhydride respectively by using dry benzene as a solvent. The FTIR of these compounds showed absorption bands at the range of (1658-1705) cm^{-1} and (1710-1770) cm^{-1} which belong to (C=O) group of lactam and lactone [19] respectively due to oxazepine ring with disappearance of absorption bands of (C=N) group at the range (1608-1593) cm^{-1} of the compounds 5-8 , . FTIR spectrum of compound 12 is shown in the figure (7)

^{1}HNMR spectrum of compound 12 figure (8) showed signals at δ 4.27 ppm (1,S, CHCO), δ 8.8 ppm (1,s, NH) , (7.57-8.18) ppm (19,m, aromatic and imine protons) and compound 13 figure (9) showed signals at δ 4.12 ppm(1,S, CHCO), δ 2.99 ppm (6,s,$N(CH_3)_2$, δ 9.68 ppm (1,s, NH), δ (6.72-8.53) ppm (19,m, aromatic and imine proton) .

Derivatives 17-19 were synthesized from the reaction of compounds 5-8 and sodium azide in tetrahydrofuran (THF) and under reflux

FTIR spectra of these compounds showed the disappearance of (C=N) group at the range (1608-1593) cm^{-1} of the compounds 5-8 and appearance of (N=N) absorbance group of tetrazole ring at the range (1469-1535) cm^{-1} [20], also the mass spectrum of compound 18 figure (10) indicated the exact mass of this compound.

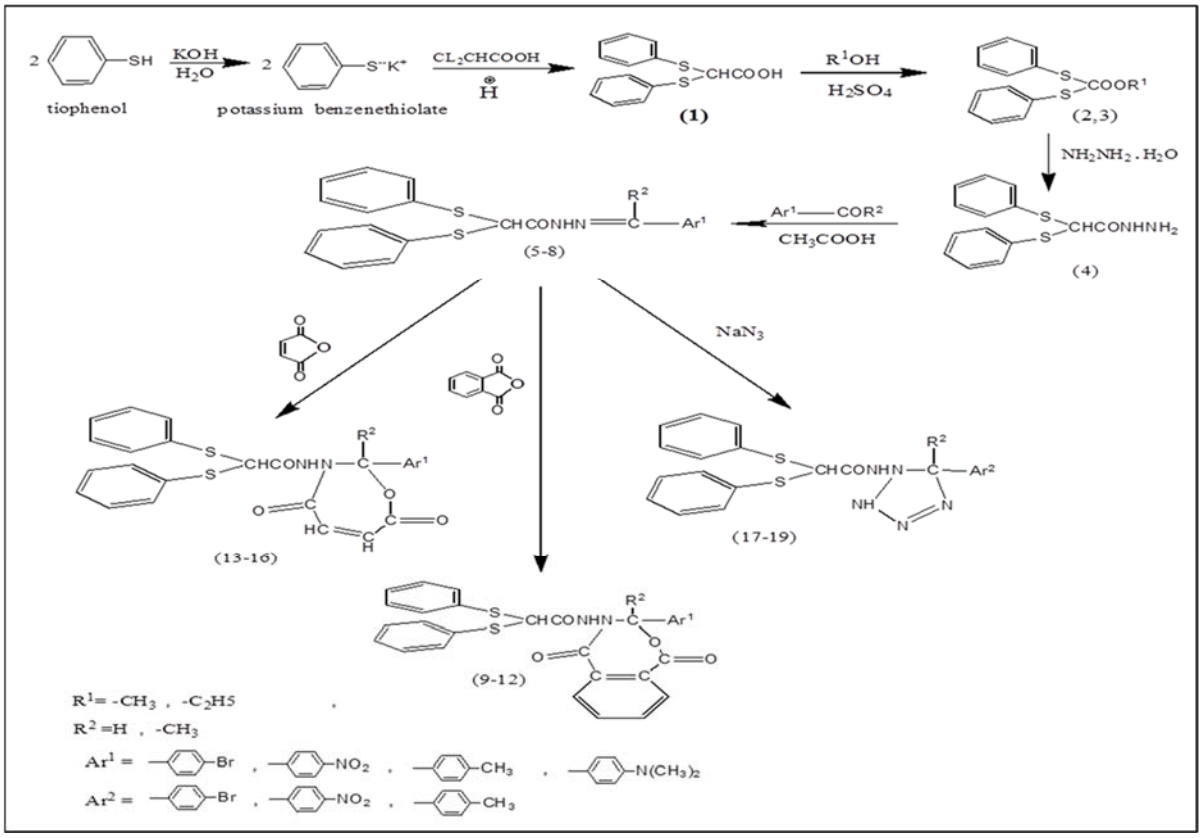
Table (2): Result of biological activity for compounds (6,7,11,16,17 & 18)

Test NO.	Comp. No.	E.coli(mm)	Staphylococcus aureus(mm)
A1	7	15	22
A2	6	7	-
A3	16	-	15
A4	11	20	17
A5	17	21	12
A6	18	18	-

Table (3): FTIR spectra data of compounds (1-19)

Comp NO.	ν (N-H)	ν (C-H) arom	ν (C-H) alipha	ν(C=O) amid	ν (C=O) lactam lacton	ν (C=C) arom	ν(C-S) thiol	νOthers
1	-	3057	2893-2958	-	-	1575	609	(C=O) str Acid 1701 (O-H) str 3057-2565 (C-O) str 1300
2	-	3005	2951	-	-	1581	613	(C=O) str Ester 1734 (C-O) Str 1280
3	-	3057	2982	-	-	1438 1579	661	(C=O) str Ester 1732 (C-O) str 1276- 1253
4	3309-3423	3062	2931	1732	-	1573	645	(C-N) str Amid 1315
5	3184	3084	2918-2989	1668	-	1579	684	(C=N) str imine 1606 (C- Br) str 630
6	3115	3047	2843-2937	1627	-	1448	630	(C=N) imine (1593) NO_2 str Sy(1514) asy(1340
7	3182	3027-3057	2920	1664	-	1535	632	(C=N) Imine 1608
8	3180	3045	2810-2908	1662	-	1523	653	(C=N) imine (1595) (C-N) str arom (1361)
9	3221	3051	2852-2989	1604	1672 1764	1583	628	(C- Br) 559
10	3100	3074	2812-2997	1675	1693 1710	1585	640	NO_2 str Sy(1404) asy(1280)
11	3160	3032	2866-2997	1616	1666 1762	1570	621	-
12	3194	3039	2808-2912	1604	1662 1739	1543	639	(C-N) str arom (1365)
13	3210	3051	2954-2854	1643	1689 1728	1585	628	(C- Br) 559 (C=C) endocyclic 1602

14	3163	3061	2897	1600	1658 1770	1442	624	NO_2 str Sy (1492) asy(1377)
								(C=C) endocyclic1554
15	3163	3051	2862- 2997	1666	1705 1724	1570	613	(C=C) endocyclic 1613
16	3120	3024	2808- 2974	1651	1705 1770	1527	605	(C-N) str arom (1342) (C=C) endocyclic 1581
17	3120	3055	2854- 2993	1647	-	1585	628	C-Br 559 (N=N) of tetrazol ring 1535
18	3115	3057	2850- 2924	1660	-	1575	620	NO_2 str Sy(1517) asy(1340) (N=N) of tetrazol ring 1469
19	3125	3059	2866- 2997	1620	-	1570	632	(N=N) of tetrazol ring 1512



Scheme (1) : The chemical steps for preparing compounds

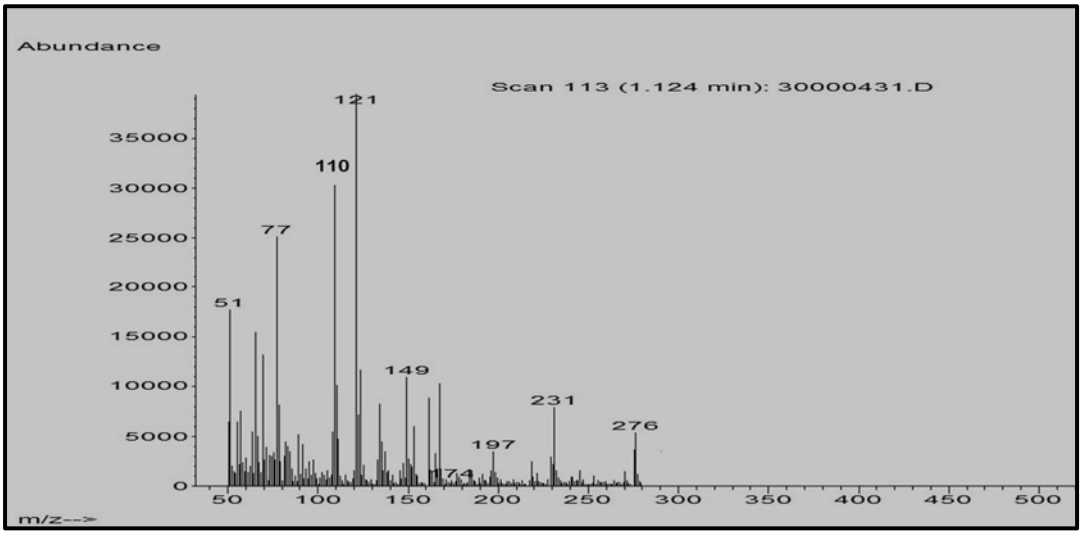


Figure (1): Mass Spectrum for compound [1]

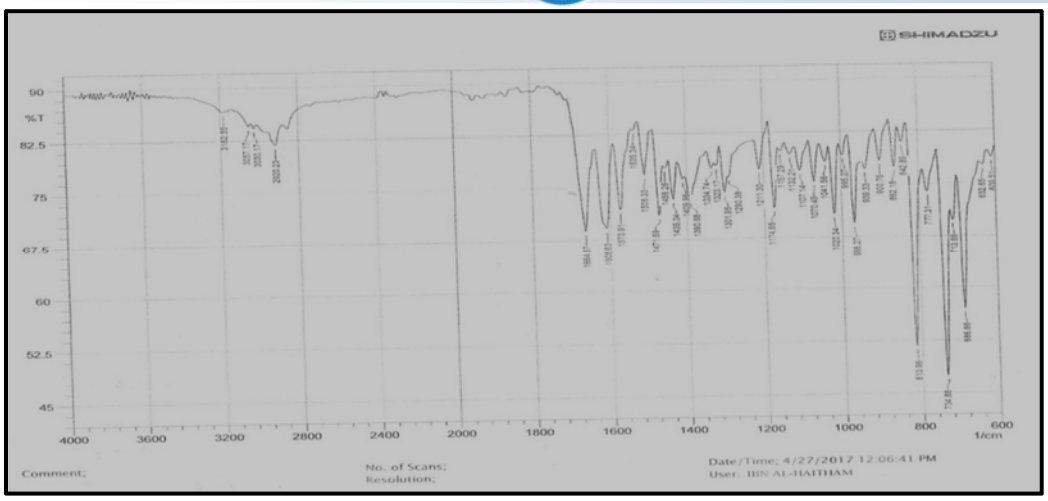


Figure (2): FTIR Spectrum for compound [7]

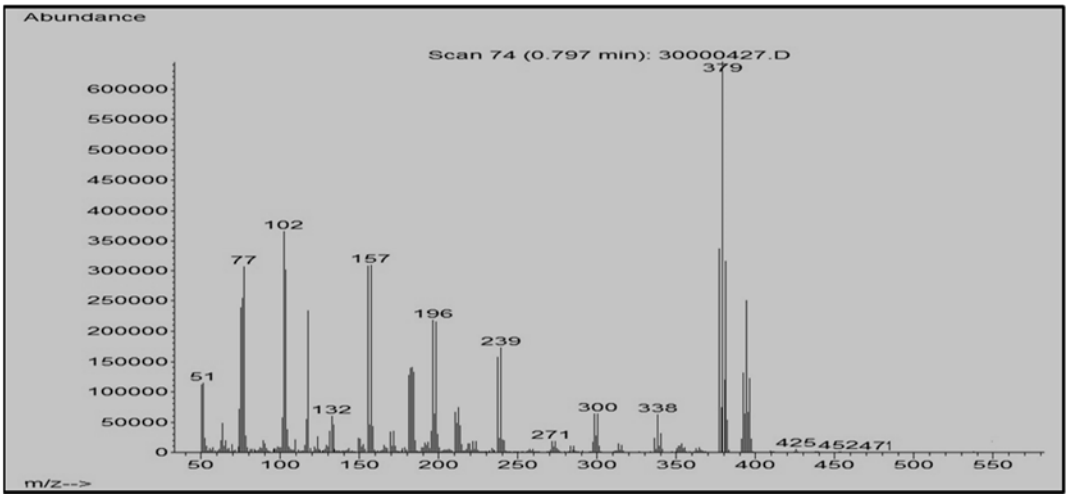


Figure (3): Mass spectrum of compound [5]

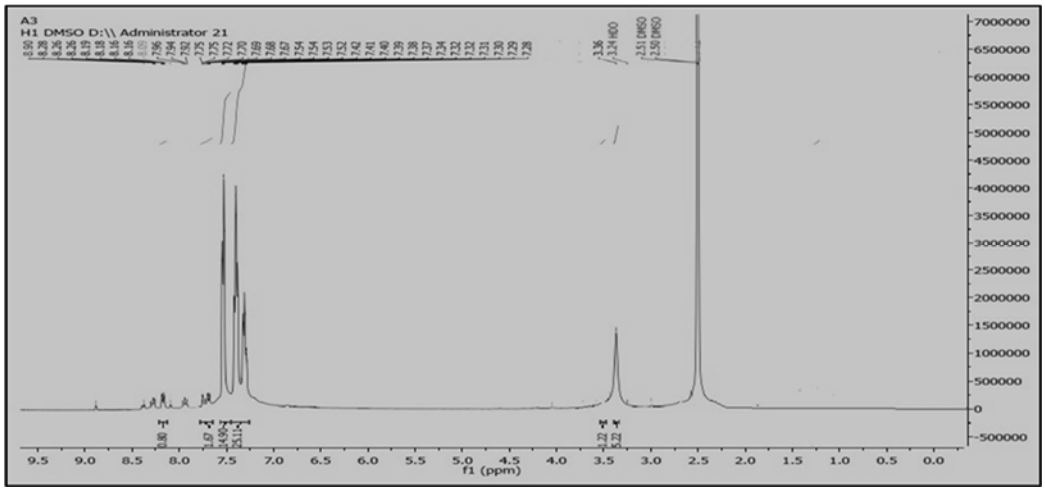


Figure (4): ^{1}HNMR Spectrum for compound (6)

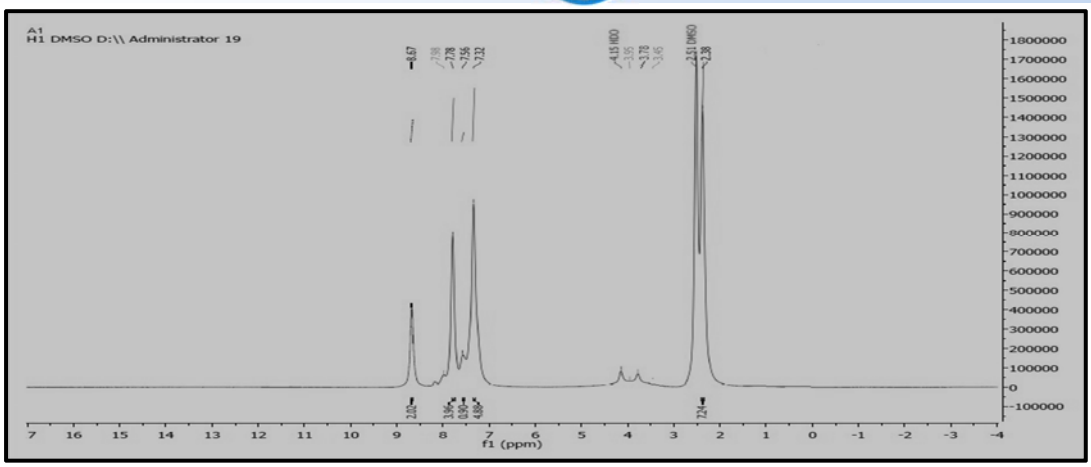


Figure (5): ^{1}HNMR Spectrum for compound (7)

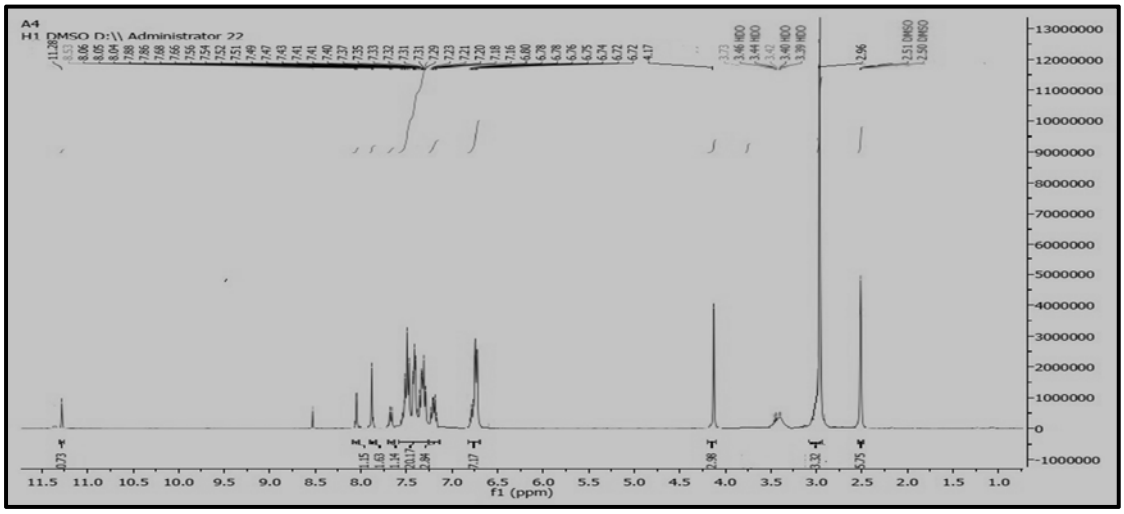


Figure (6): ^{1}HNMR Spectrum for compound (8)

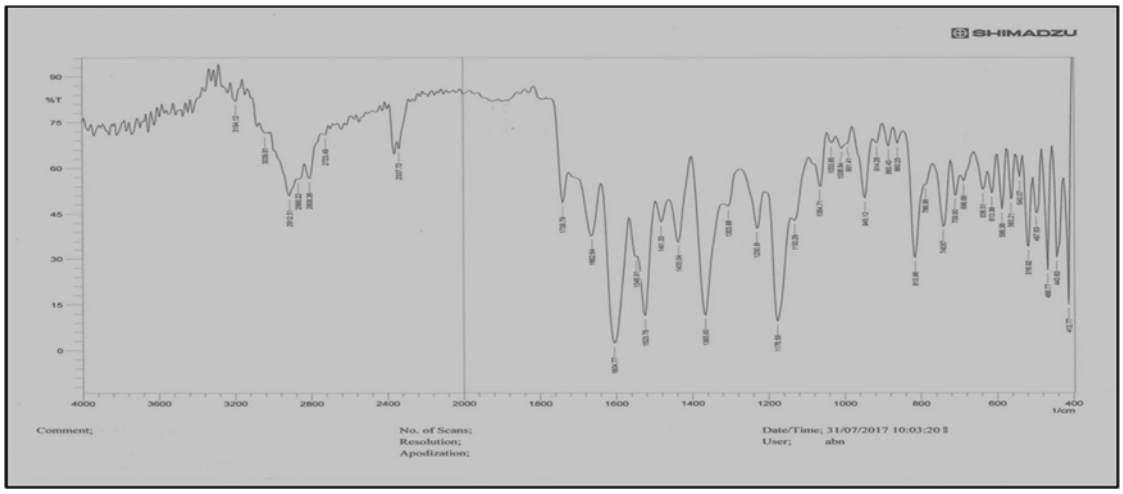


Figure (7): FTIR Spectrum for compound (12)

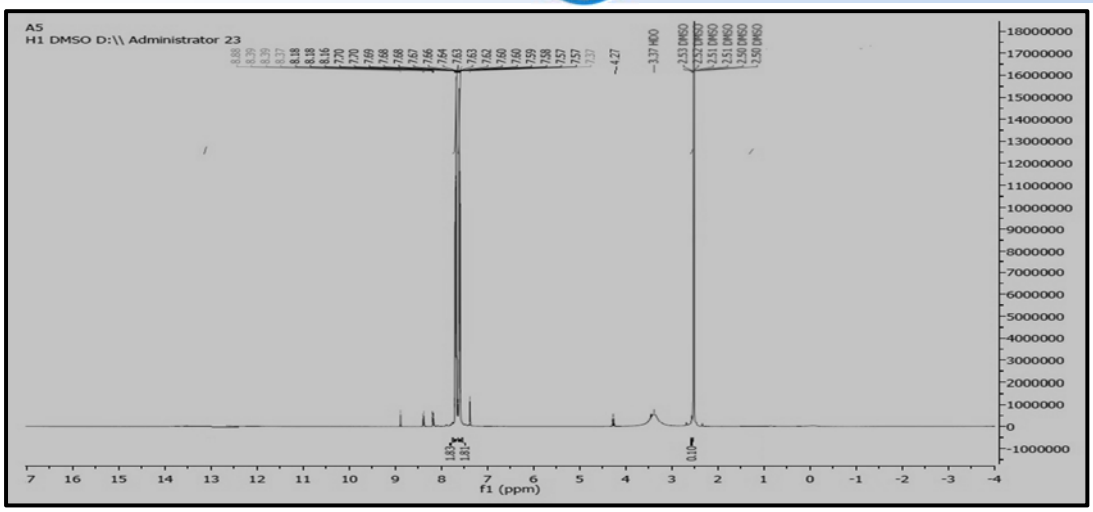


Figure (8): ^{1}HNMR Spectrum for compound (12)

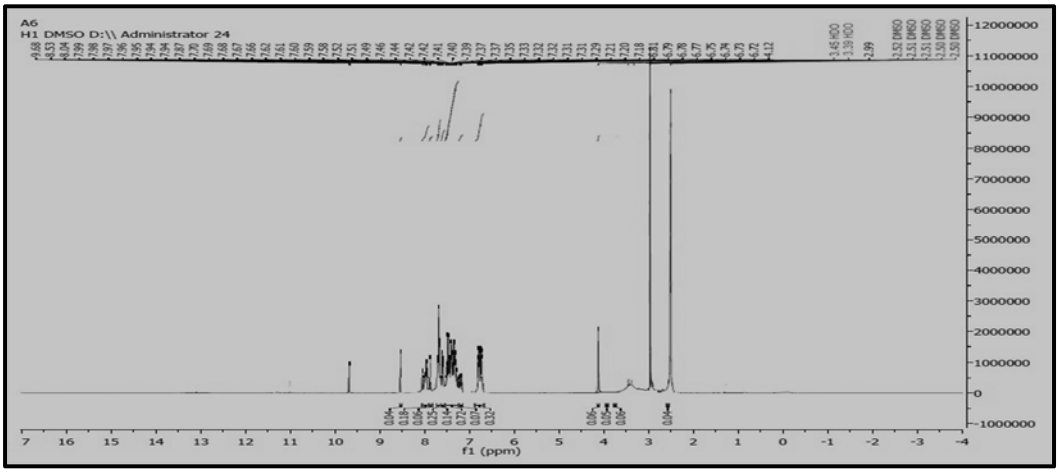


Figure (9): ^{1}HNMR Spectrum for compound (13)

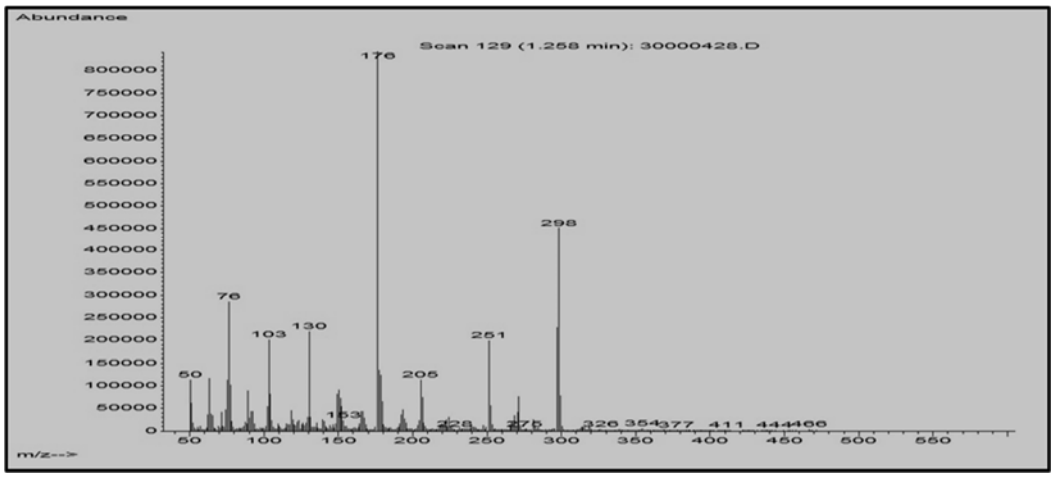


Figure (10): Mass spectrum of compound (18)

Biological activity

The effect of compounds 6, 7, 11, 16, 17 and 18 prepared in (10% DMF solution) were tested against two types of bacteria *Escherichia coli* and *staphylococcus* aurous the experiment was operated by using nutrient agar plates. The plates were incubated at (37) c for (24) hrs. The study showed all compounds have a differing biological activity on mentioned bacteria accept compound 17 has no biological activity toward the *E. coli* and compounds 7and19 have no activity toward *staphylococcus aurous* and compound 16 have no activity toward Escherichia coli. table (2).

References

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