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Synthesis of Some New Schiff Bases Starting from 2,2 Dimorpholinyl Acetic Acid and Evaluating the Biological activity

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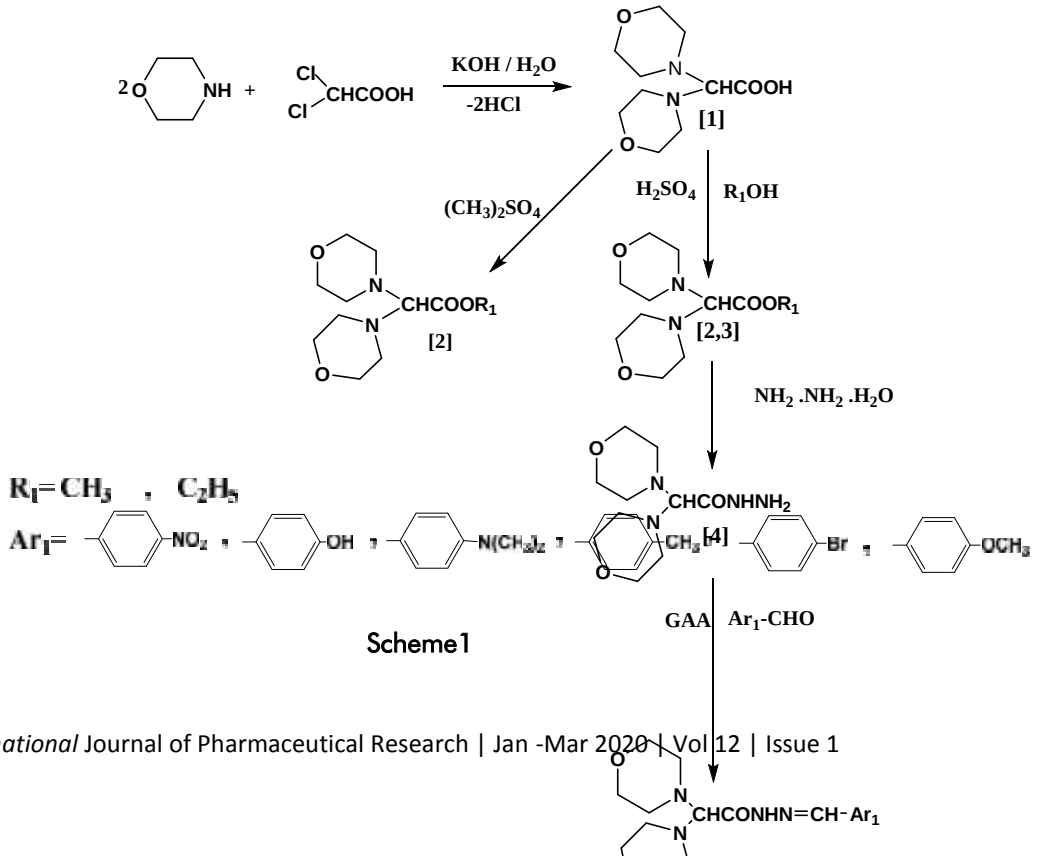
ABSTRACT
In this study new derivatives of Schiff bases (5-10) were synthesized from the new starting material 1 . Which has been synthesized by the reaction of (1 mol.) of dichloroacetic acid with two moles of morpholine, in the presence of potassium hydroxide, Ester derivatives 2 and 3 were synthesized by the reaction of 1 with methanol or ethanol respectively in the presence of sulphuric acid as catalyst . Compound 2 was also prepared from dimethylsulphate with high yield , 2 and 3 was used to synthesized 2,2-dimorpholinylacetohydrazide 4 via reaction with $NH_2NH_2.H_2O$ 80% .Imines (5-10) were synthesized via the reaction of 4 with appropriate aromatic aldehydes in the presence of G.A.A as a catalyst . Derivatives compounds (1-10) were identified by FT-IR and some of them by ^{1}H-NMR and mass spectroscopy . The biological activity of new derivatives (5-10) was examined against two kinds of bacteria *E. coli (G-)*, *Staph. aureus (G+)*. Some of these compounds was found to be vital activity against the selected bacteria.

Keyword: Morpholine, Dichloroacetic acid, Acid hydrazide, Schiff bases, biological activity.

INTRODUCTION

Morpholine is one of heterocyclic secondary amines and it is afairly strong base. It is the most weidely used in organic synthesis and in industry [1,2]. It is represent an important building block of some typical secondary metabolites like Timolol, linezolid, Emorfazoneand alkaloid polygonafolin [3,4] Morpholine derivatives have great importance in heterocyclic chemistry because of its significat and potent biological activities such as antibacterial, anticancer, antimalarials analgesic and anticovulsant [5-10]. Schiff bases are the compounds posing azomethine group (-HC=N) and it reported at the first time by Hugo Schiff [11]. It have been considerably significant in organic synthesis. There are different kinds of reaction in which imines have been found extremely serious applications [12-15]. Schiff base have more importance in biological or therapeutic employments. Many of these derivatives were found to have a vital activity such as anticancer, antiviral agent, antifungal and anti-inflammatory [16-20]. In this work we intend to synthesis new derivatives of Schiff bases derived from the new compound 2,2-dimorpholinylacetic acid that it was synthesized from dichloroacetic acid.



Scheme1

Chemicals

All compounds were providing by Aldrich , Merck and Fluka chemicals companies .

Techniques

The melting points were measured on Gallenkamp device and were uncorrected. FT-IR spectra were recorded as KBr disc by Shimadzu FT-IR 8400 spectrometer in the range 4000-600 cm^{-1}.The ^{1}H-NMR spectra were acquired in DMSO-d_6 as a solvent by a Bruker 400 MH_Z spectrometer with (TMS) tetra methyl silane as an internal standard. Mass spectra of derivatives were measured on GCMS QP Gas Chromatography mass spectrometer, Agilent Technology (HP).

Synthesis

The steps for synthesis new compounds (1-10) are summarized in the Scheme 1. The nomenclature, physical properties and yield of all new compounds listed in Table .

B)

Compound **1** (0.5g, 2.173mol) was dissolved in dry acetone(50mL),then (0.2 g, 0.001mol) of anhydrous sodium carbonate was added, the mixture of reaction was stirred for (15 minutes). After that dimethyl sulphate (0.27mL) hasbeen carefully. The reaction mix refluxed for (24 hrs),and followed by (TLC). The mixture was filtered over anhydrous magnesium sulphate then the filtrate was filtered again & the solvent was removed under reduced pressure to afford **2** as semisolid,yield (80%) .

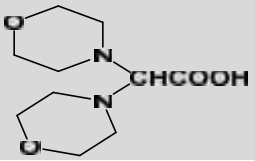
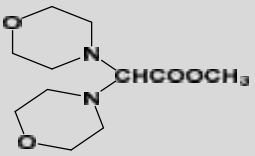
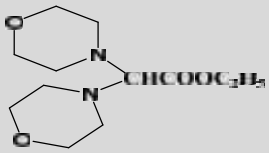
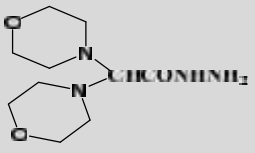
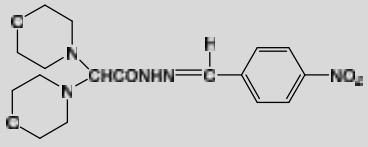
-Synthesis of 2,2-dimorpholinylacetohydrazide 4[24]

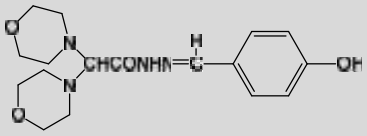
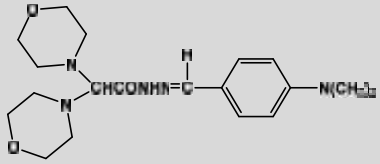
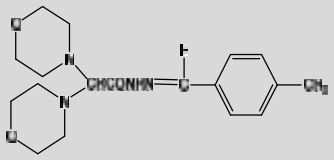
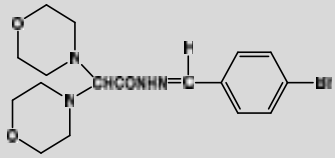
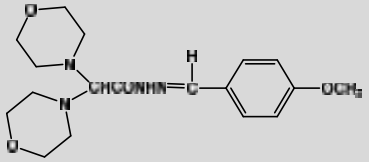
Ester derivative **2** (0.5g, 2.04mol) or **3** (o.5g, 1.93mol) was dissolved in (30mL) of ethanol with (2ml) of hydrazine hydrate 80% . The reaction mix was refluxed for (24hrs). Later the resulting solution was cooled and the precipitate was filtered & recrystallized from absolute ethanol to produce **4**m.p>300 °C, output (60%). Table (1) show the physical properties for acid hydrazide**4**.

Synthesis of Ń-(Substituted methylene-2,2-dimorpholinylacetohydrazide (5-10) [25]

Derivative **4** (0.5 g , 0.002 mol.) was dissolved in (30 mL) of abs.EtOH& then appropriate aldehyde (0.30 mol.)with (2-3) drops of CH_3COOH was added gradually to the mix. The reaction mix was refluxed for (8-9) hrs. After the reaction was completion (monitored by TLC) and cooled to room temperature, the precipitate was filtered off & recrystallized from abs. EtOH. Table (1) shown the physical properties for the derivatives(5-10).

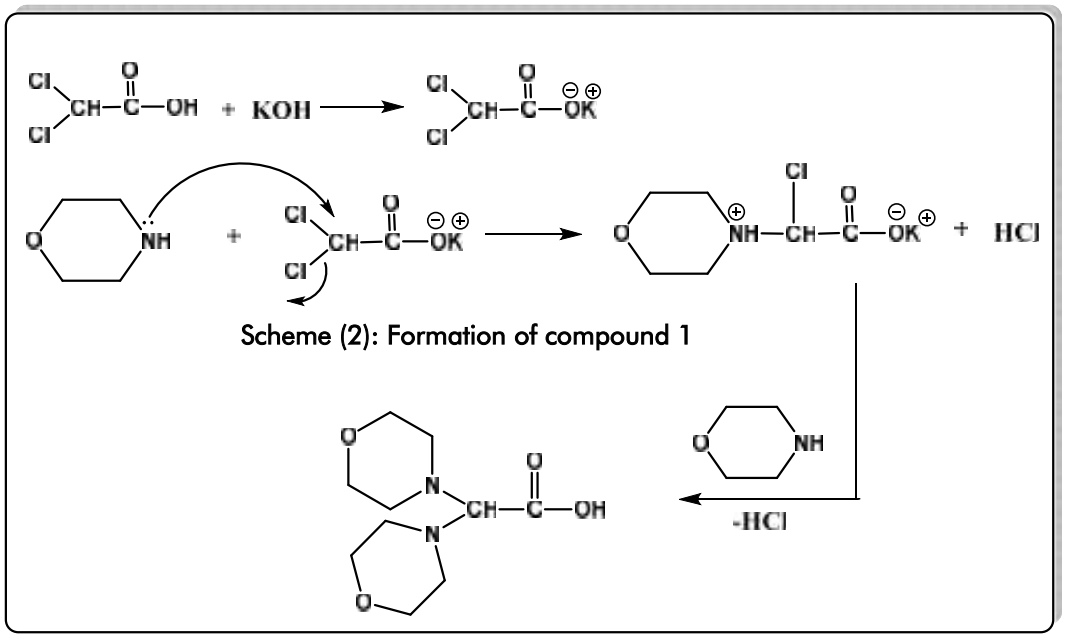
Table (1): Physical properties of compounds (5-10)

Comp. Number	Comp. structure	Nomenclature	Molecular Formula	M.W g/mol	M.p °C	Yield %	Color	Solvent recryst.
1		2,2-dimorpholine acetic acid	$C_{10}H_{18}N_2O_4$	230	100	85	yellow	acetone
2		methyl 2,2-morpholinyl acetate	$C_{11}H_{20}N_2O_4$	244	oily	30	brown	ethanol
3		ethyl 2,2-morpholinyl acetate	$C_{12}H_{23}N_2O_4$	259	oily	40	brown	ethanol
4		2,2-dimorpholinyl aceto hydrazide	$C_{10}H_2N_4O_3$	244	>300	60	white	ethanol
5		2,2-dimorpholine-N –(4-nitro benzylidene) acetohydrazide	$C_{17}H_{23}N_5O_5$	377	70	45	yellow	ethanol

6		N'-(4-hydroxybenzylidene)-2,2-dimorpholinoacetohydrazide	$C_{17}H_{24}N_4O_4$	348	75	40	brown	ethanol
7		N'-(4-(dimethylamino)benzylidene)-2,2-dimorpholinoacetohydrazide	$C_{19}H_{29}N_5O_3$	375	55	60	brown	ethanol
8		N'-(4-methylbenzylidene)-2,2-dimorpholinoacetohydrazide	$C_{18}H_{26}N_4O_3$	346	95	70	brown	ethanol
9		N'-(4-bromobenzylidene)-2,2-dimorpholinoacetohydrazide	$C_{17}H_{23}BrN_4O_3$	410	40	75	brown	ethanol
10		N'-(4-methoxybenzylidene)-2,2-dimorpholinoacetohydrazide	$C_{18}H_{26}N_4O_4$	362	130	80	brown	ethanol

RESULTS AND DISCUSSION

Compound **1** was synthesized by the reaction of (2 mol.) of morpholine with (1 mol.) of dichloroacetic acid in the presence of KOH . This reaction was performed according S_N2 mechanism in which two chlorine atoms was eliminated as2HCl and replaced by two groups of morpholine [26] Scheme (2).



Scheme (2): Formation of compound 1

Compound **1** was produced in high yield 85% and having m.p.100°C. Its FT-IR spectrum Figure (1) displayed obvious absorption peaks at (3350-2500)cm^{-1} refers to υ (OH) group of acid & at (1620)cm^{-1} belong to υ(C=O). Another absorption bands appeared at (2981)cm^{-1} and (2866)cm^{-1} due to (C-H) ofaliphatic groups. All the other absorption bands were registered in the Table (2). Mass spectrum of the new acid Figure (2) a and b gave the accurate molecular ion at (m/z =230.4). Compound **2**,**3** were synthesized from the reaction of new acid derivative **1** with methanol or ethanol respectively using concentrated sulfuric acid as a catalyst . In this method compound 2 or 3 were yielded in low ratios (30-40)% . Another method was used to prepare . **2** with high yield of 80% by the reaction of compound 1 with dimethyl sulfate [27]. FTIR spectra for compound **2** and **3** figures (3) and (4) showed absorption peaks refers to frequency of carbonyl group for ester at (1737-1751)cm^{-1}, υ(C-O) ester at (1274,1292)cm^{-1} respectively with vanishing of absorption bands due to frequency of carbonyl group for acid at (1620)cm^{-1} and frequency of hydroxyl group for acid at (3400-2500)cm^{-1}. All FT-IR spectral data were summarized in Table (2) 2,2-dimorpholinylacetohydrazide 4 was synthesized by the reaction of compound **2** or **3** with $NH_2NH_2.H_2O$ 80% in EtOH under reflux. The FTIR spectrum of acid hydrazide**4** figure (5) showed absorption bands at (3475)cm^{-1} and at (3325,3186)cm^{-1} due to symmetric and asymmetric stretching of υ(NH-NH_2) group [28] with disappearance of bands at (1737,1751)cm^{-1} refers to υ(C=O) belonging to the two derivatives of ester and at (1274,1292)cm^{-1} due to υ(C-O-C) for ester.The FTIR showed other absorption packs at (1627)cm^{-1} and at (2981,2840)cm^{-1} refers to υ(C=O) amide and υ(C-H) aliphatic respectively. All spectral information is included in the Table (2).New materials (5-10) were synthesized by the condensation of acid hydrazide**4** with various aromatic aldehydes in the presence of glacial acetic acid. The FTIR spectra for materials (5-10) figures (6), (7), (8), (9), (10) and (11) indicated the vanishment of bands at (3475)cm^{-1} and (3325,3186)$cm^{-1}$of the υ(NH-NH_2) group with occurrence of new bands at rang between (3105-3197)cm^{-1} belong to the NH group. Other absorption bands appeared at (1697-1597)cm^{-1} , (1654-15554)$cm^{-1}$and at (1531-1445)cm^{-1} refers to υ(C=O) amide, υ(C=N) imine and υ(C=C) of aromatic rings. The rest of the main spectral absorptions are listed in the Table (2) . The mass spectra of compounds **5** and **6** figures (12) a , b and (13) gave the set molecular weight at m/z =377.4 and m/z = 348 respectively . The ^{1}HNMR spectrum of compound 7 figure (14) is shown δ2.73 ppm (6H, S, $N(CH_3)_2$, δ2.99 PPM (16H , aliphatic ring protons), δ(6.59-7.89) ppm (4H,dd, aromatic and imine(CH=N) protons), δ8.5 ppm (1H, S, NH). ^{1}HNMR spectrum of compound 8 fig. (15) is shows δ1.23 ppm (3H, S, CH_3), δ2.51 ppm (16H , aliphatic ring protons), δ(7.2 – 7.83) ppm (4H, dd, aromatic and imine (CH=CN) protons) δ8.67 ppm (1H, S, NH). Compounds (5-10) were tested versus two kinds of pathological bacteria *E. coli* and *staph. aurous*. The resultsshowed that some of these compounds gave a different response to the selected bacteria compounds **8** and **9** have no activities toward two types of these bacteria. Table (3) shown the biological activity data for compounds (5-10).

Table (2): FTIR spectra data of compounds (1-10)

Comp. NO.	V(N-H)	V(C-H) arom.	V(C-H) alipha.	V(C=O) amid.	V(C=C) arom.	V(C=N) imine	V Others
1	-	-	2981,2866	-	-	-	(C=O) str Acid 1620 (O-H) str 3400-2500 (C-O) str 1103 (C-N) str 1303
2	-	-	2954,2854	-	-	-	(C=O)str Ester 1737 (C-O) str ether 1114 (C-O) str ester 1274 (C-N) str 1352
3	-	-	2980, 2900	-	-	-	(C=O)str Ester 1751 (C-O) str ether 1064 (C-O)str ester 1292 (C-N) str 1373
4	3475	-	2951,2840	1627	-	-	(C-N) str 1284
5	3105	3047	2943,2845	1675	1531	1600	(NO_2) str 1342 (C-N) str1292
6	3163	3097	2981,2885	1670	1445	1585	(C-N) str amid1219 (C-O) str 1157
7	3197	3032	2904, 2808	1597	1516	1554	(C-N) strarom 1303 (C-N)str amid 1226
8	3120	3032	2920,2854	1685	1508	1616	(C-N) str amid 1288
9	3190	3032	2974,2873	1697	1481	1654	(C-N) str amid 1203 (C-Br) 1006
10	3194	3005	2962,2839	1685	1462	1597	(C-N) str amid 1257 (C-O) str 1157

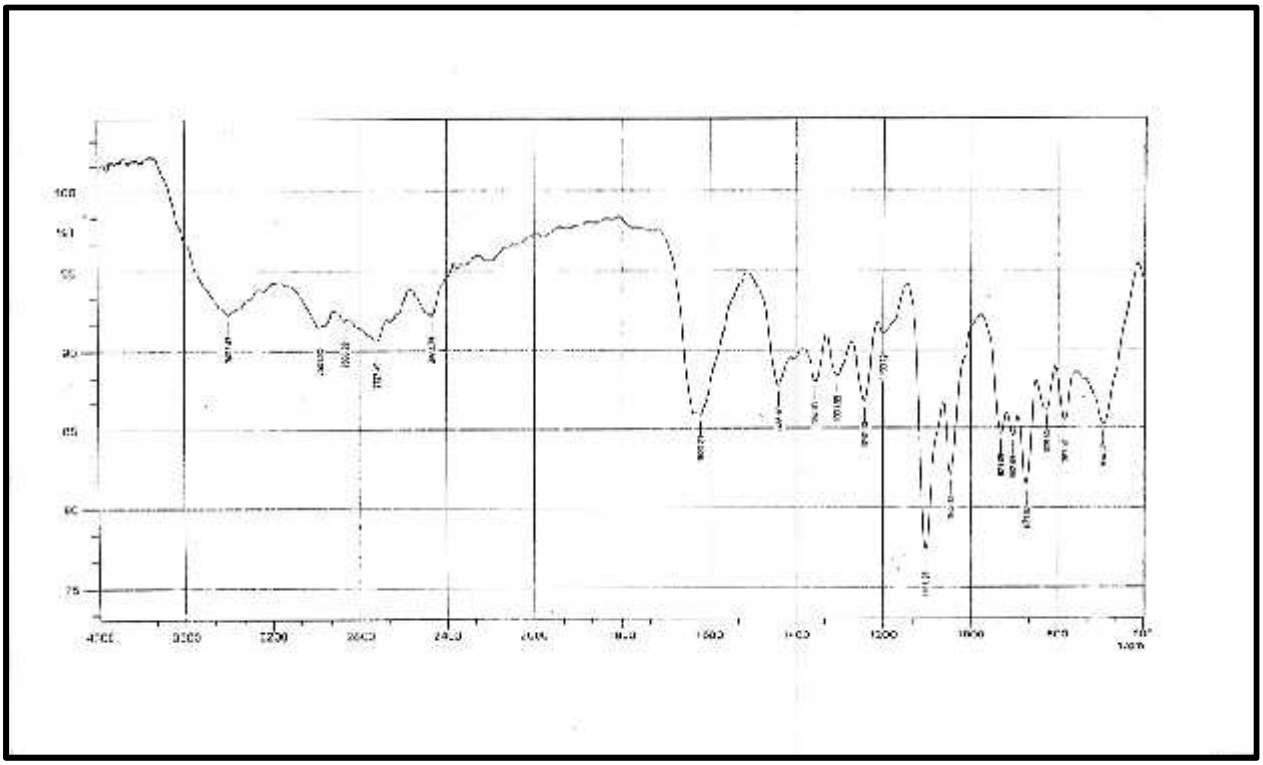


Fig. (1): FTIR Spectrum of1

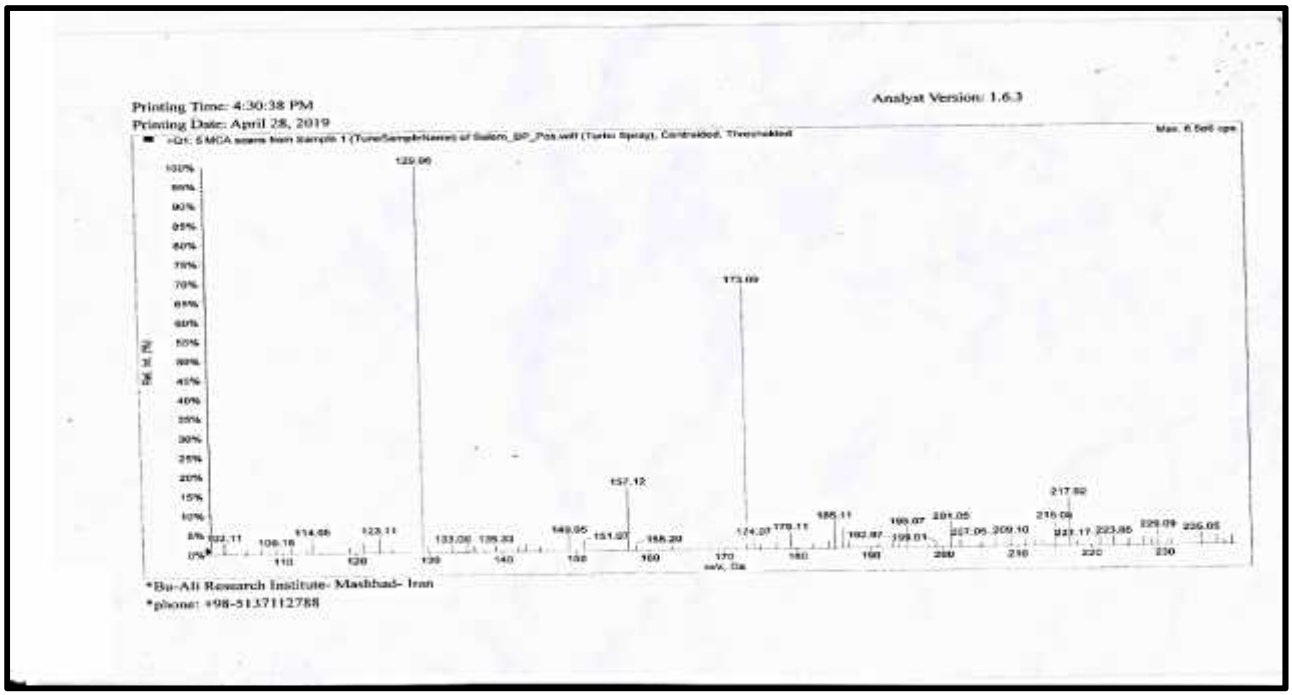


Fig. (2):(a) Mass Spectrum of 1

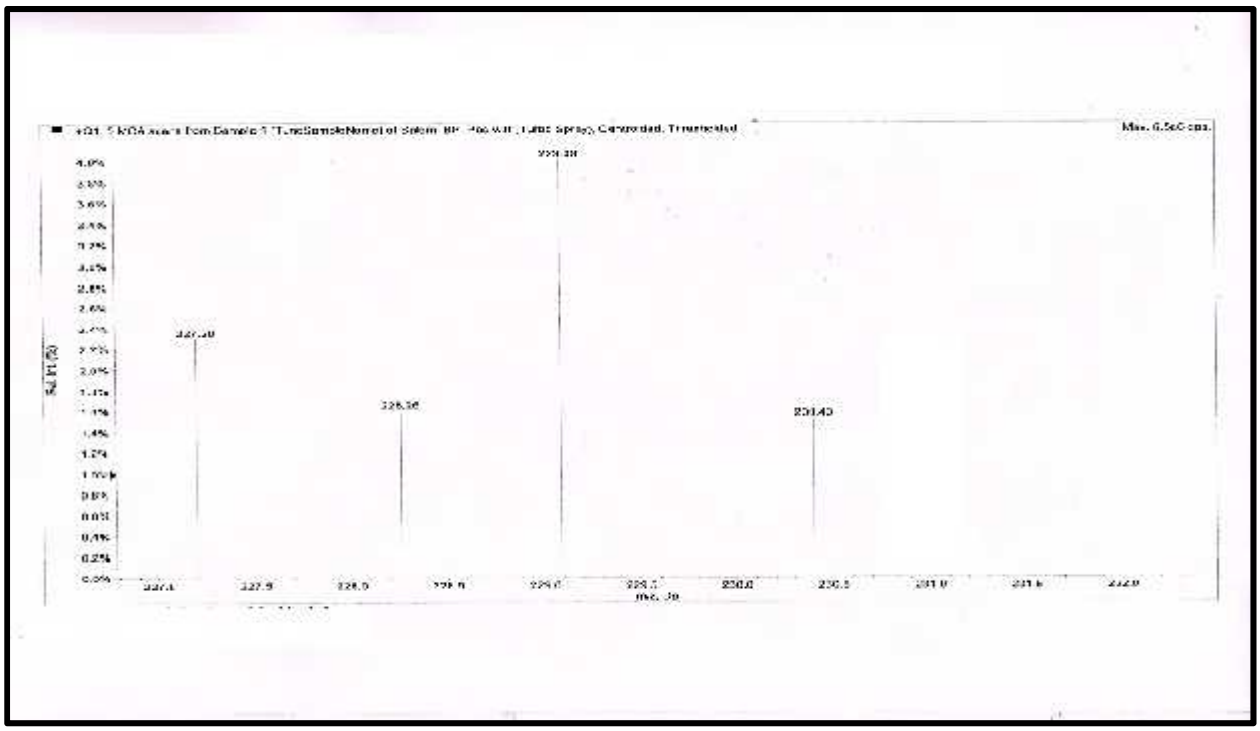


Fig. (2):(b) Mass Spectrum of 1

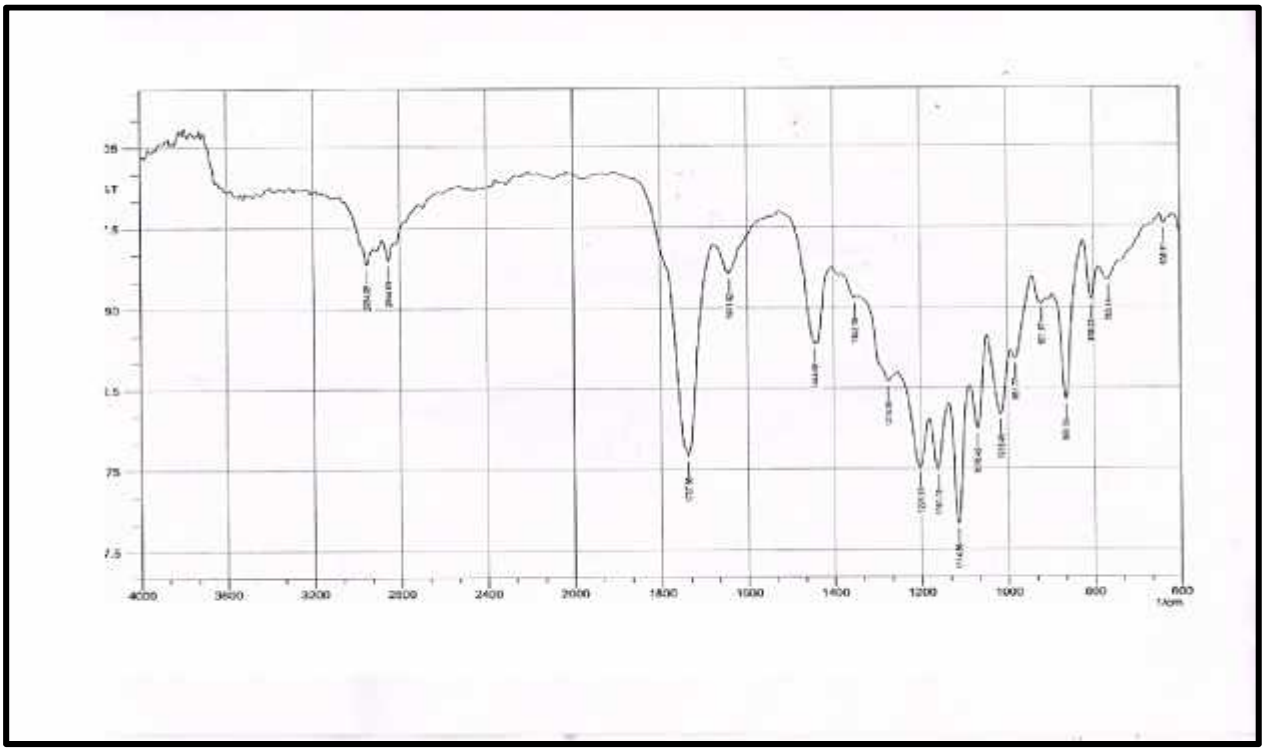


Fig. (3): FTIR Spectrum of2

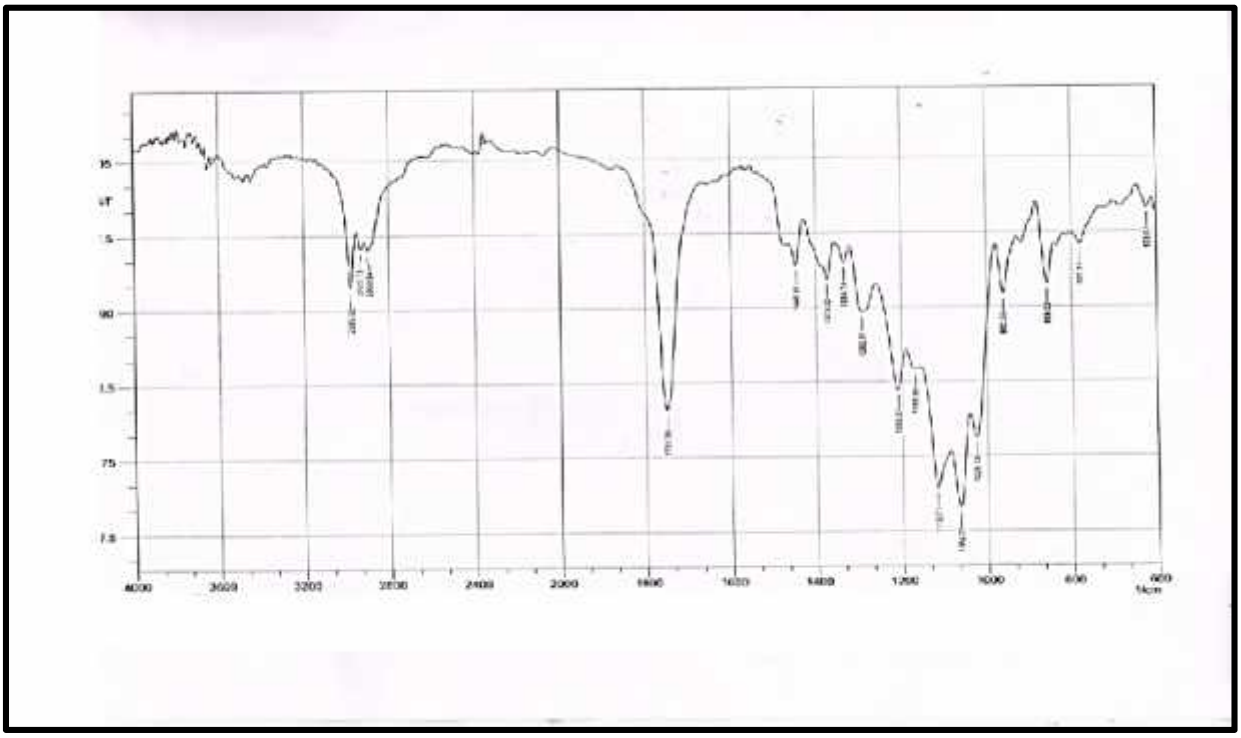


Fig. (4): FTIR Spectrum of 3

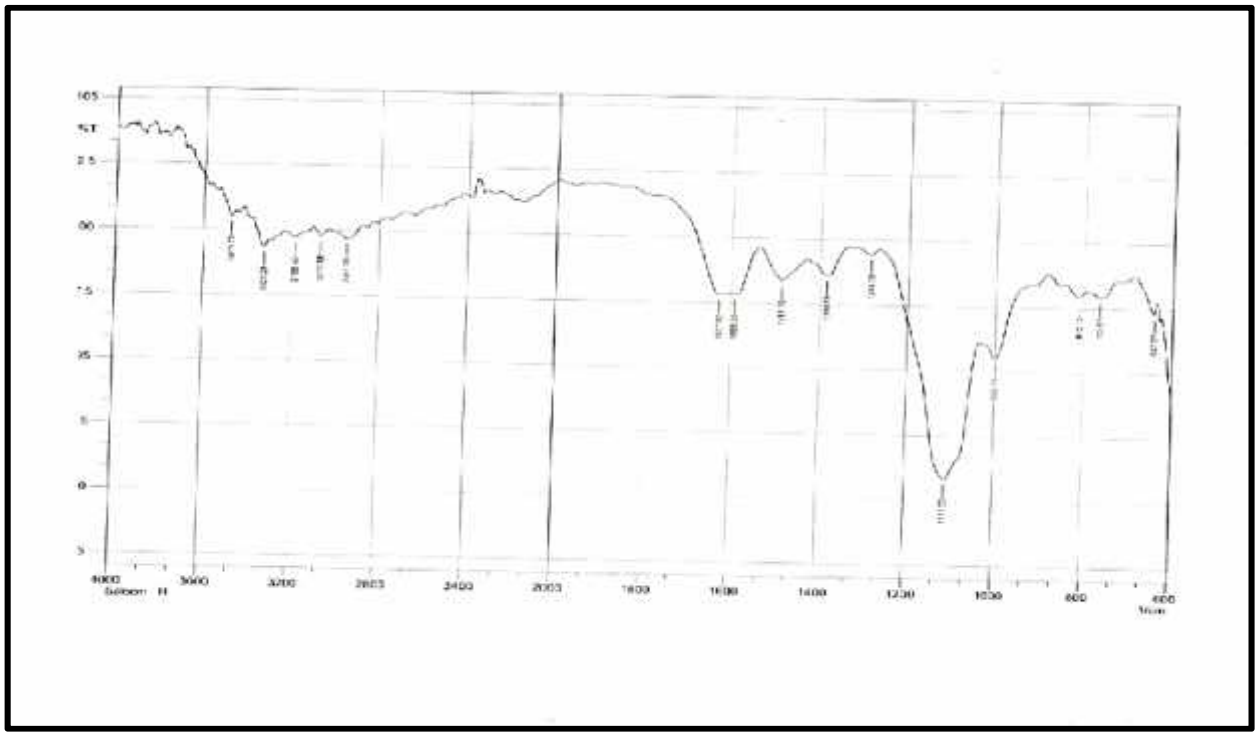


Fig. (5) : FTIR Spectrum of 4

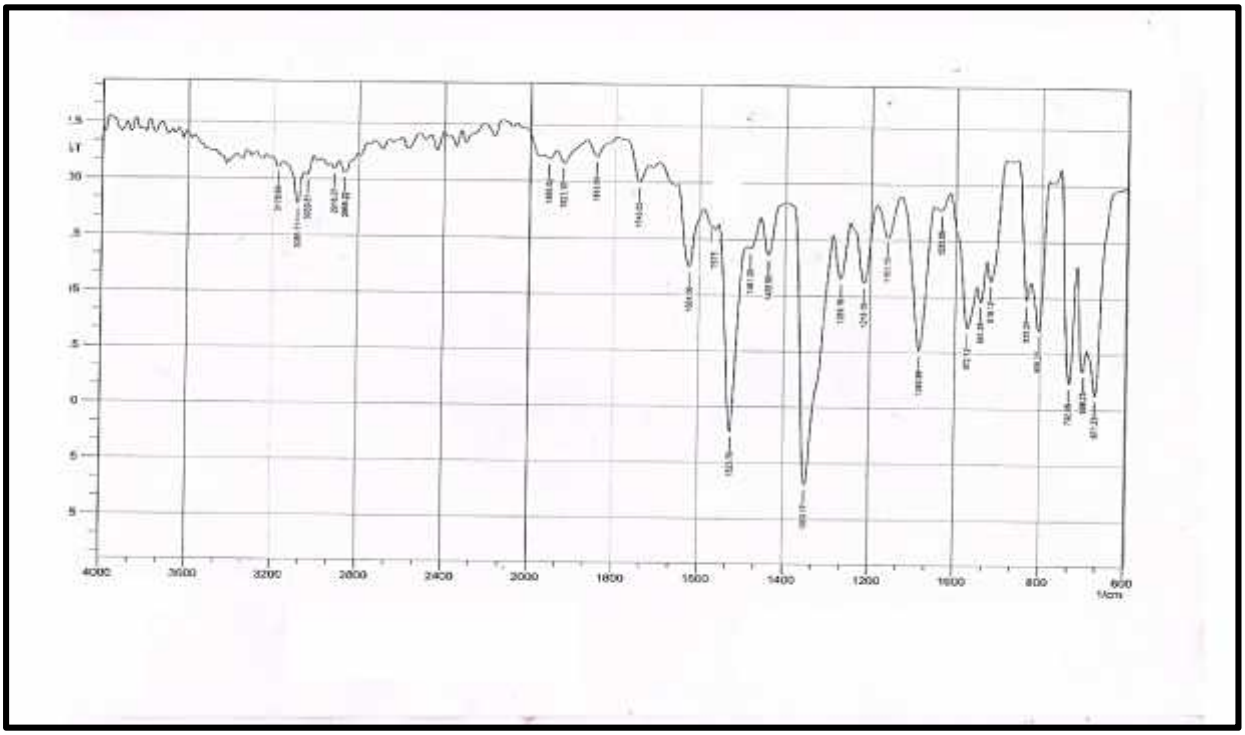


Fig. (6) : FTIR Spectrum of5

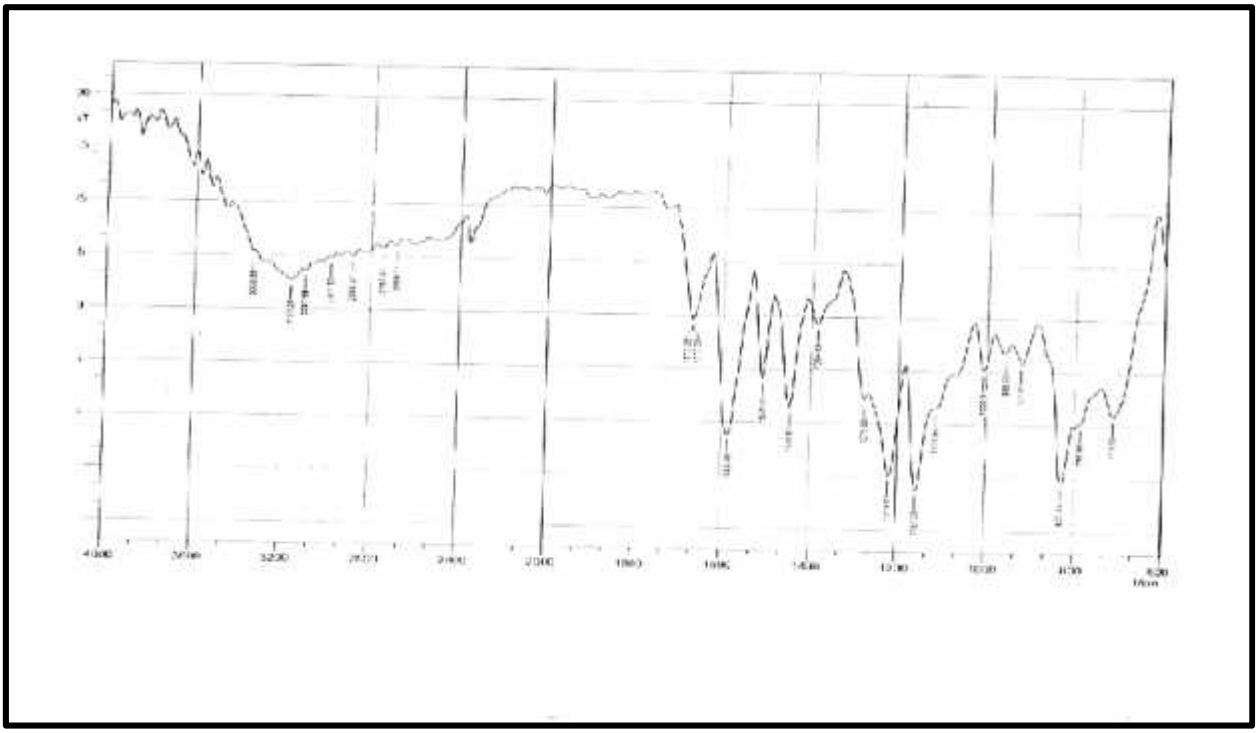


Fig. (7) : FTIR Spectrum of 6

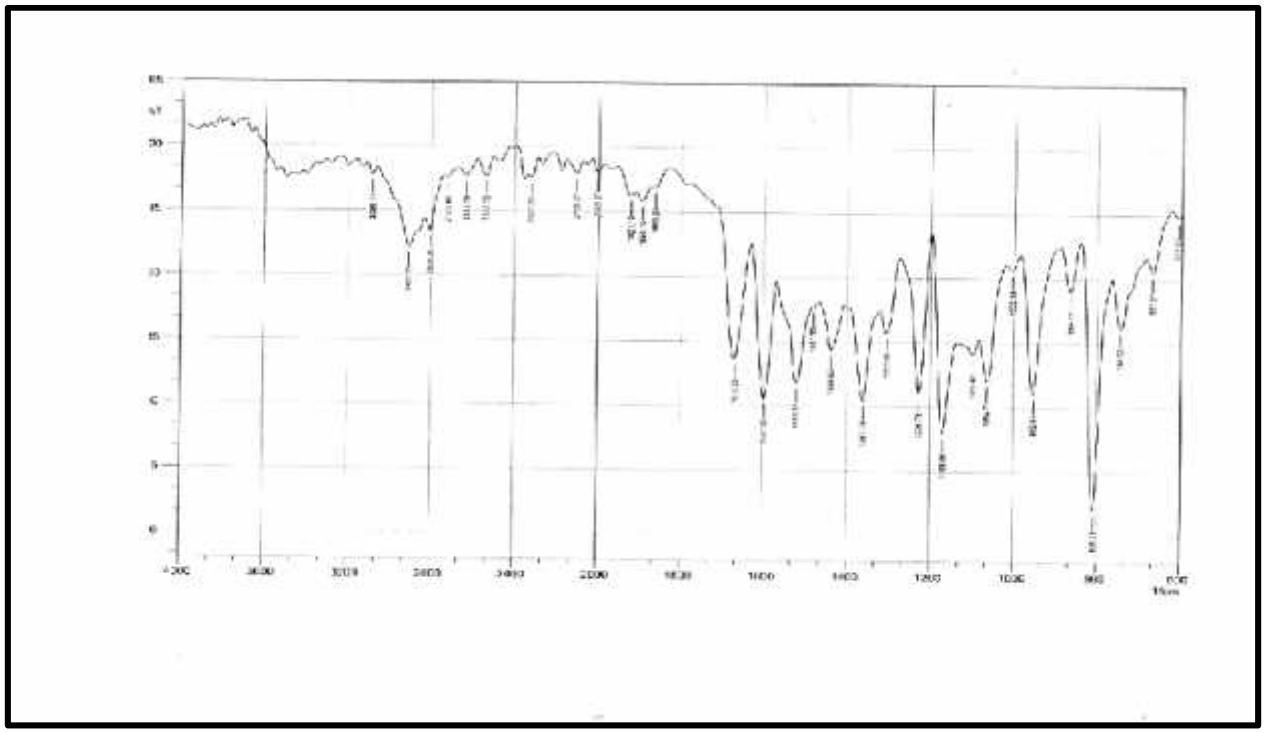


Fig. (8): FTIR Spectrum of 7

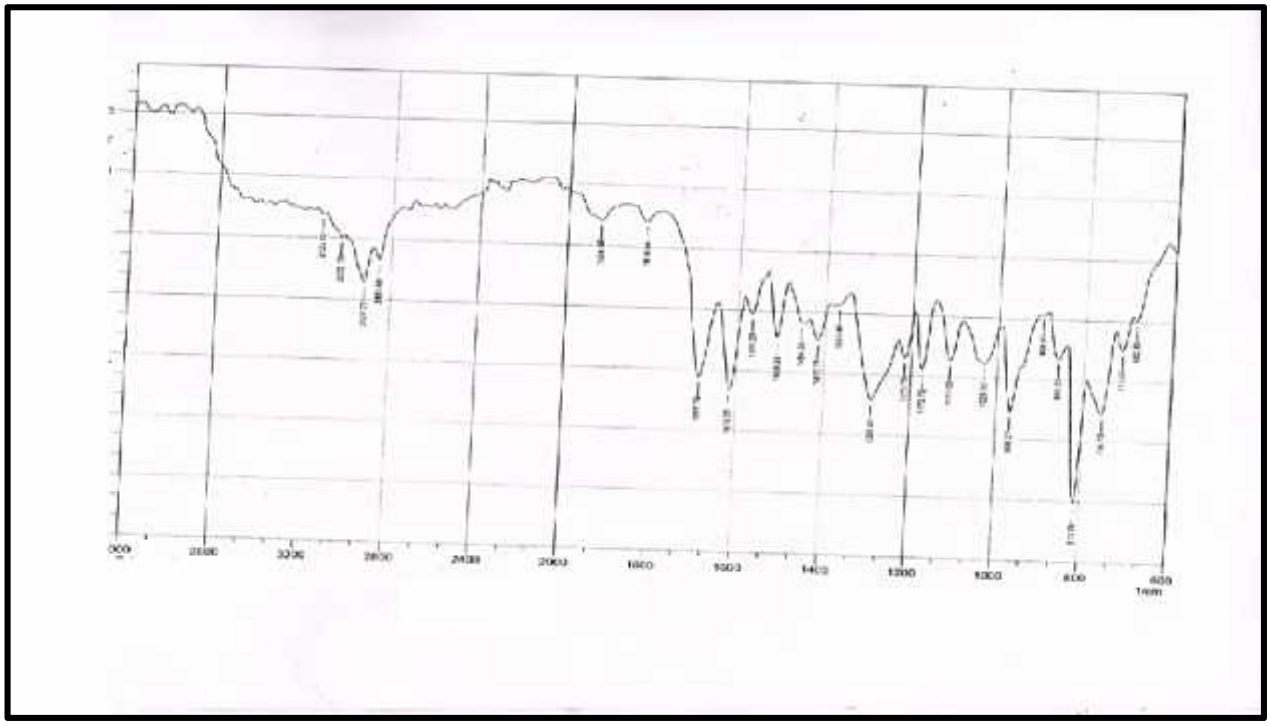


Fig. (9): FTIR Spectrum of 8

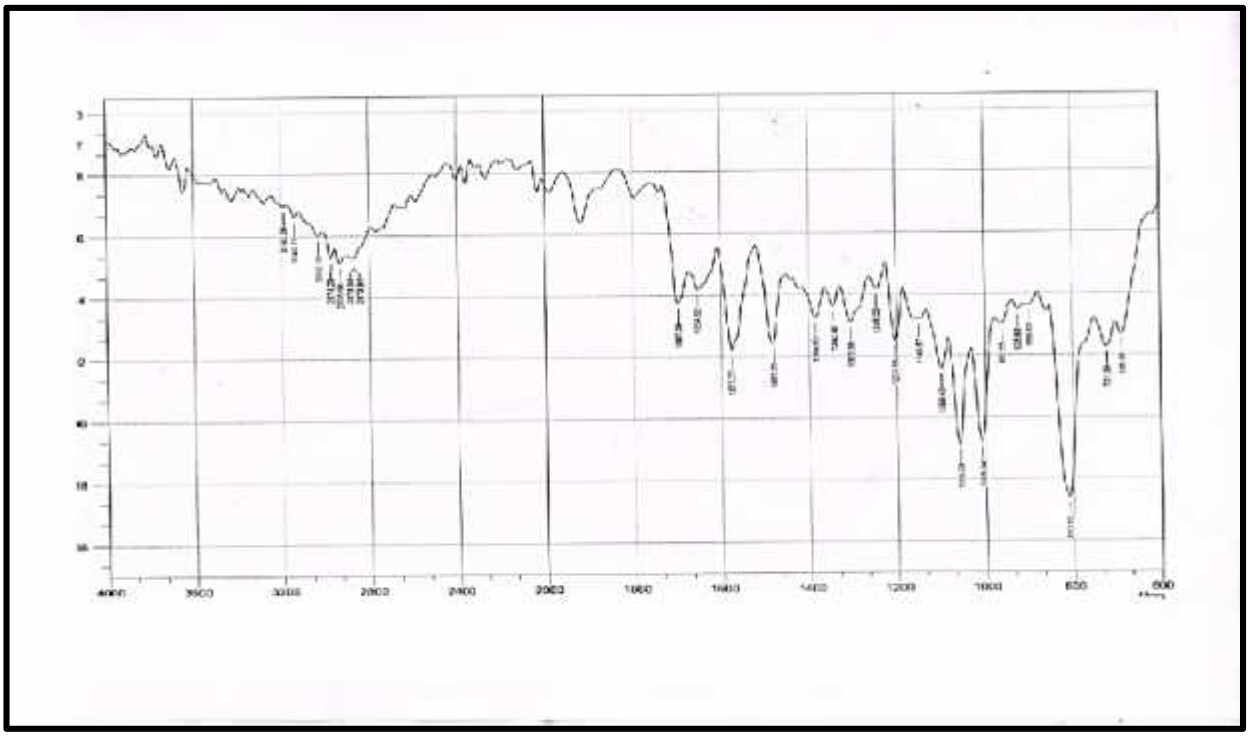


Fig. (10): FTIR Spectrum of9

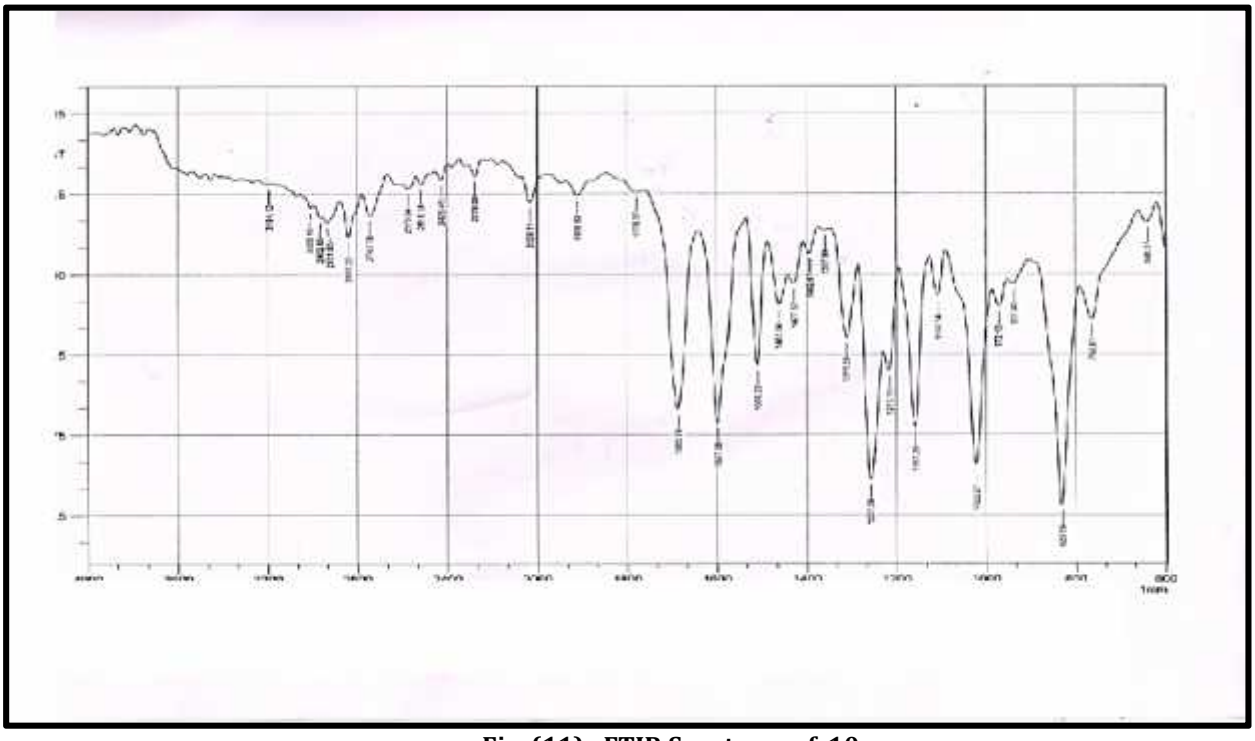


Fig. (11) : FTIR Spectrum of 10

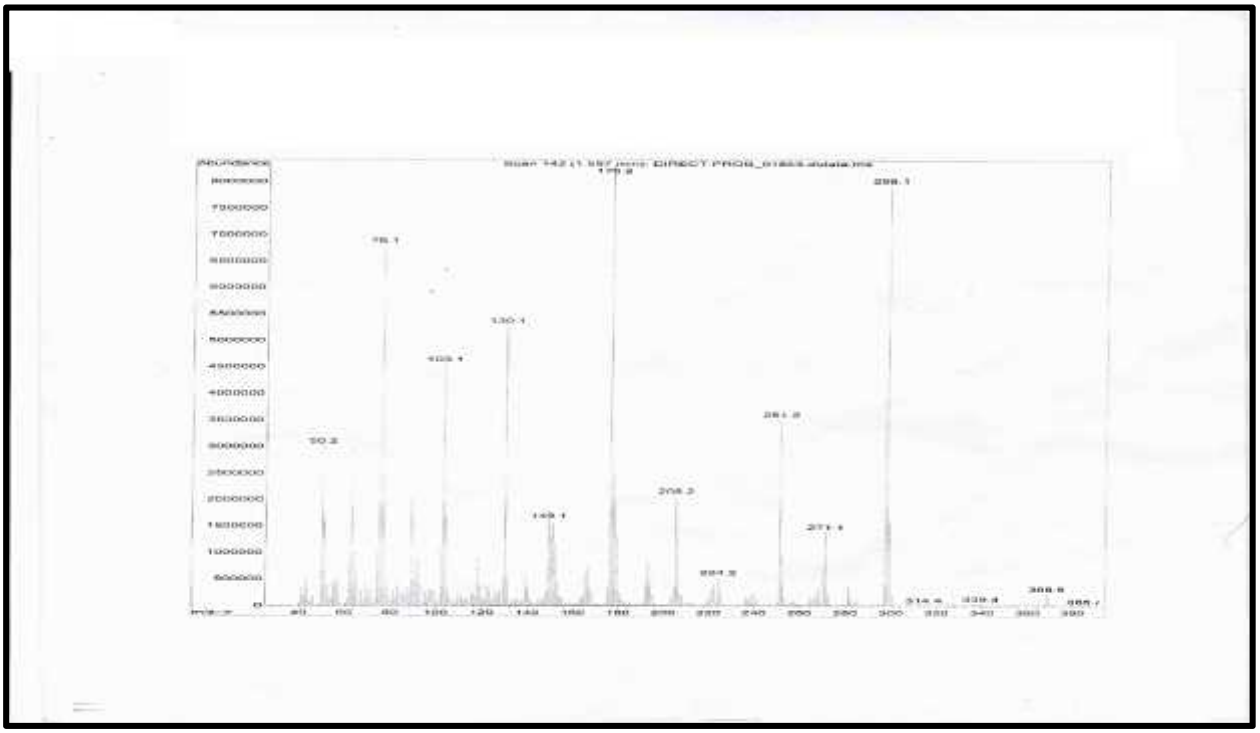


Fig. (12):(a) Mass Spectrum of 5

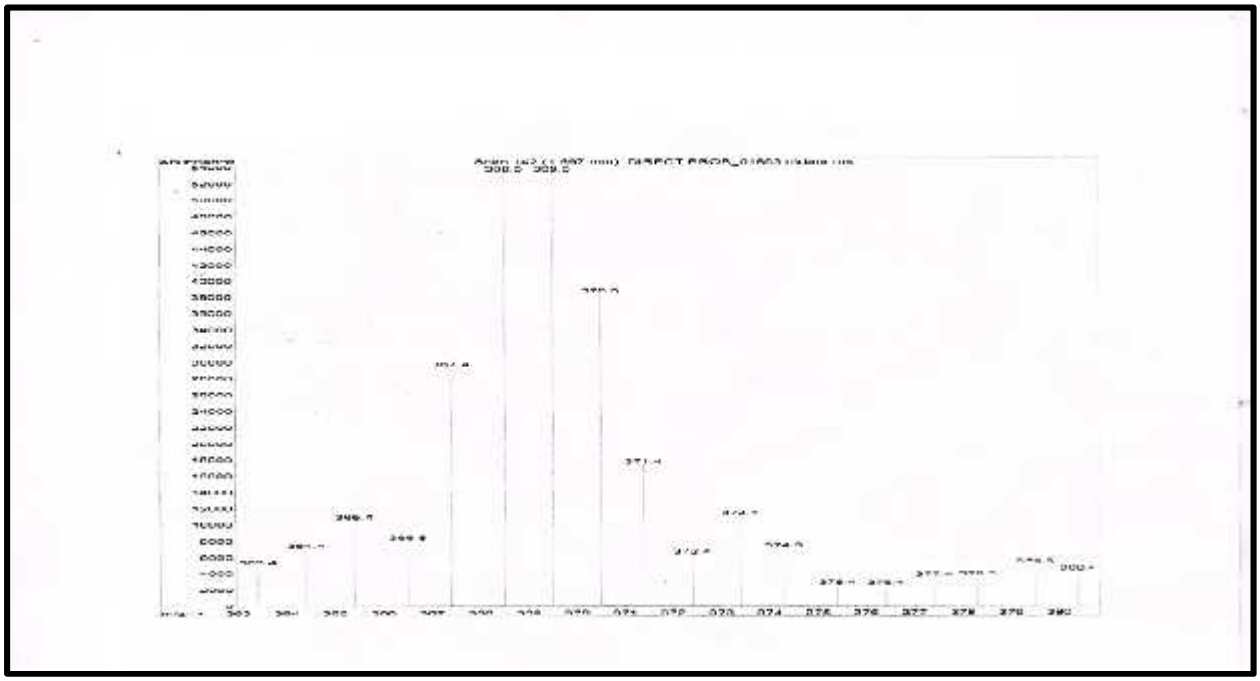


Fig. (12):(b) Mass Spectrum of 5

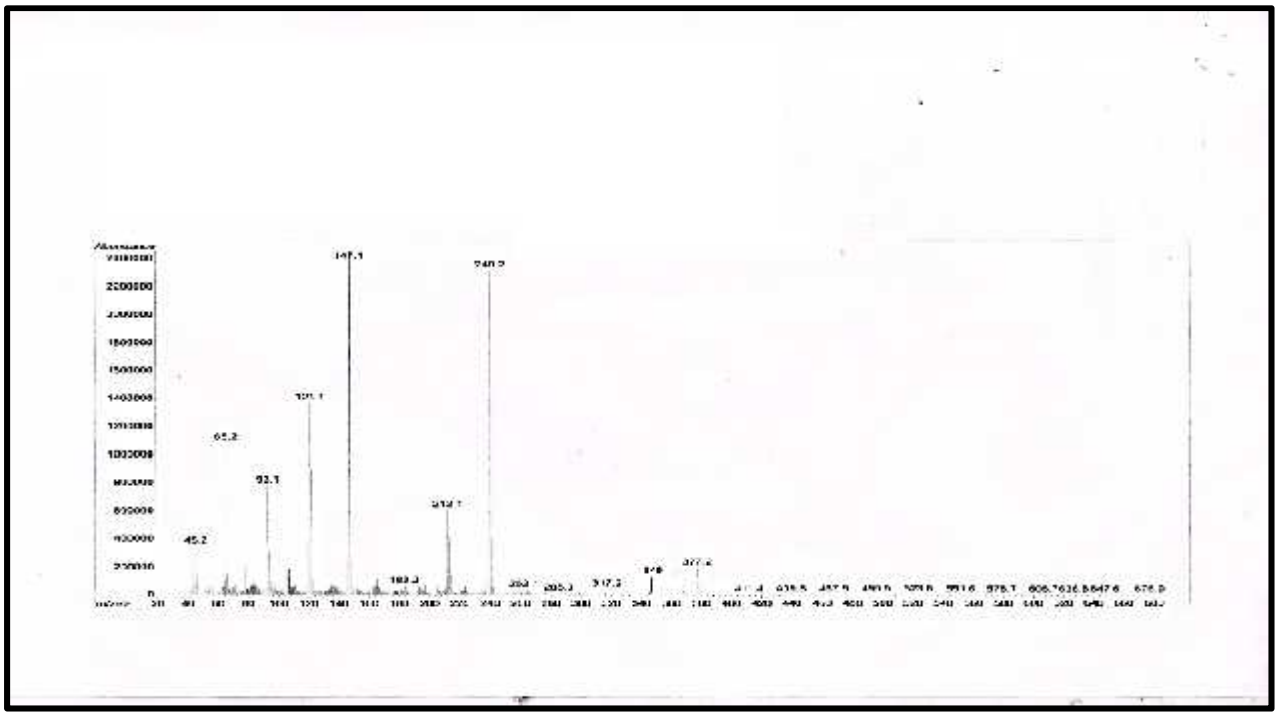


Fig. (13): Mass Spectrum of 6

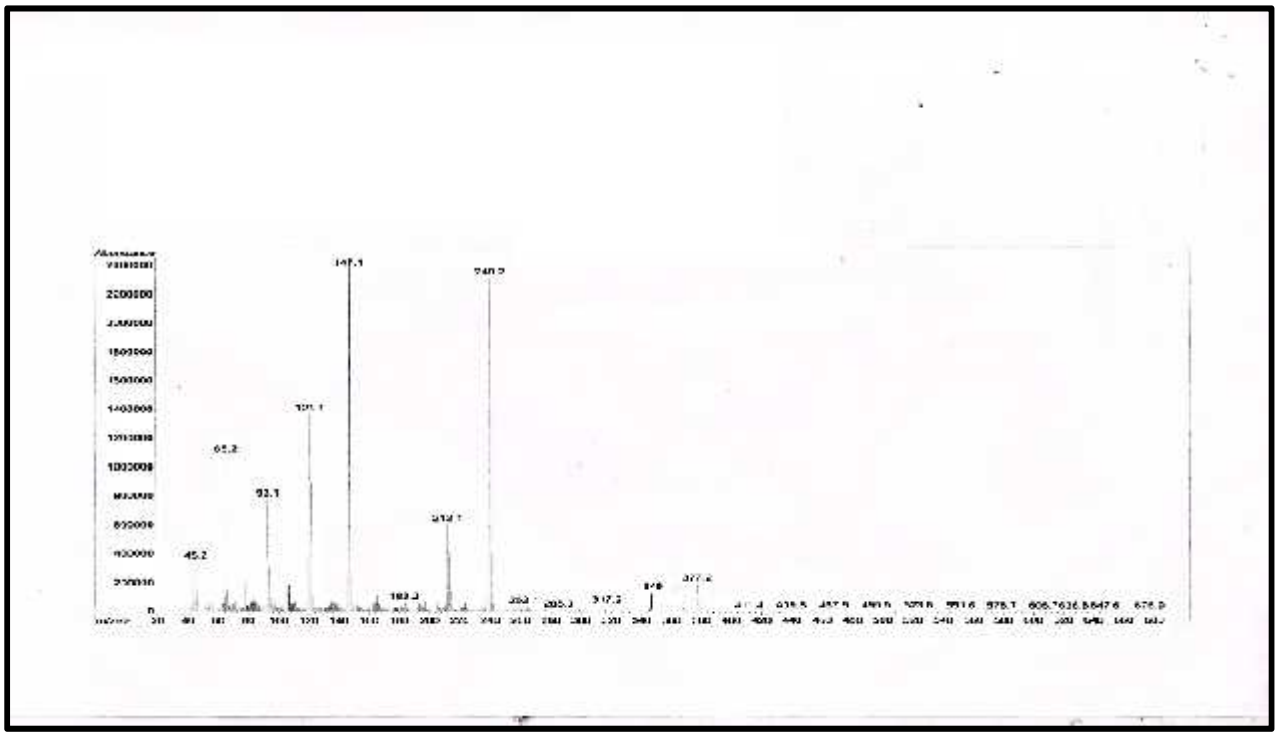


Fig. (14): ^{1}HNMR Spectrum of 7

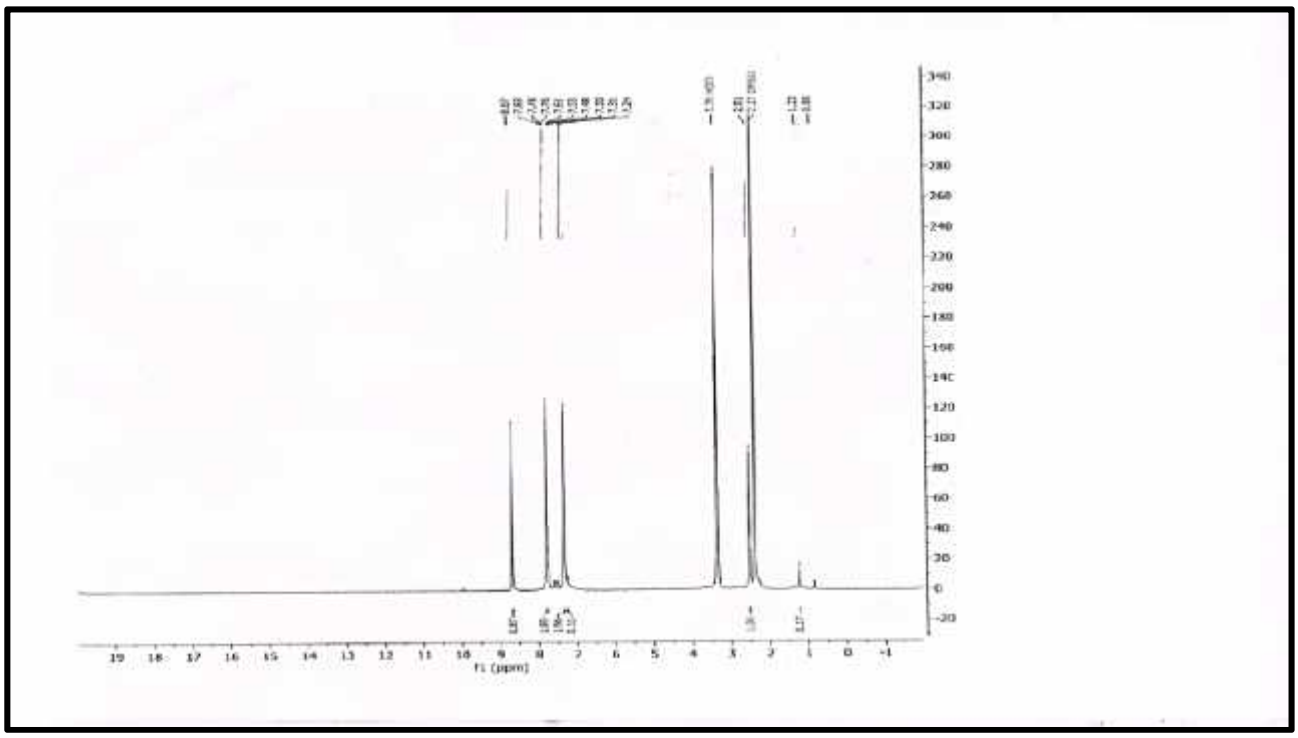


Fig. (15): ^{1}HNMR Spectrum of 8

Table (3): Results of vital activity of compounds (5-10)

Comp. No.	*E. coli (G-)* (mm)	*Staph. Aureus(G+)*(mm)
5	-	18
6	10	13
7	-	13
8	-	-
9	-	-
10	14	14

Key of the table : control= 5mm , low active =6 – 9 mm , good active = 10 – 15 high active= 16 – 20 , symbols (-) = inactive .

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