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MICROWAVE ASSISTED SYNTHESIS AND BIOLOGICAL EVALUTION OF SOME NOVEL COUMARIN SCHIFF BASES

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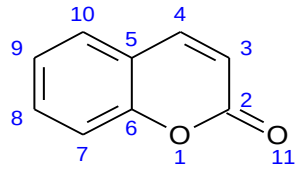
ABSTRACT

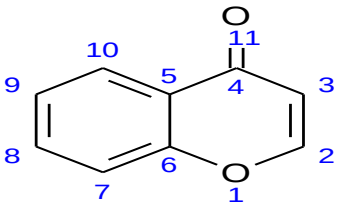
The present work involves the synthesis of some novel schiff base derivatives synthesized from 7-hydroxy-4-methyl coumarin. A series of coumarin Schiff bases were prepared by adding equimoles of 7-hydroxy-4-methyl coumarin with equimoles of different aromatic amines. All the synthesized schiff base derivatives were characterized by using analytical techniques (FT-IR, ^{1}H NMR and C^{13}NMR Spectroscopy). The title compounds were evaluated for antibacterial activity against Gram-positive bacteria (Staphylococcus aureus and Bacillus subtilis) Gram-negative bacteria (Escherichia coli and Proteus valgaris) and antifungal activity against (Pencilliumchrysogenum, Pencilliumnotatum and Aspergillus niger). Coumarin Schiff base derivatives (1-14) were synthesized in good yields and showed good antimicrobial activities. Among them the compounds 1,2,6,8,12 were significantly active against gram positive, gram negative bacteria. Compounds 1,11,12,14 were shown good anti-fungal activities. The rest of compounds showed moderate to weak activity.

INTRODUCTION:

Coumarins owe their class name to ‘Coumarou’, the vernacular name of the tonka bean (Dipteryxodorata Willd.,Fabaceae), from which coumarin was isolated in 1820[1]. Coumarin is classified as a member of the benzopyrone family of compounds, all of which consist of a benzene ring fused to a pyrone ring . The benzopyrones are subdivided into the benzo-α-pyrones and benzo-γ-pyrones. Coumarins belongs to the benzo-α-pyrones. Coumarins occupy an important place in the realm of natural products and synthetic organic chemistry[1,2]. Coumarins have important effects in plant biochemistry and physiology, as they act as antioxidants, enzyme inhibitors, and precursors of toxic substances.



2*H*-1-benzopyran-2-one



4*H*-1-benzopyran-4-one

In addition, these compounds are involved in the actions of plant growth hormones and growth regulators, the control of respiration, photosynthesis, as well as defense against infection[3].

Coumarins have long been recognized to possess anti-inflammatory, anti-oxidant, anti-allergic, hepatoprotective, anti-thrombotic, anti-viral and anti-carcinogenic activities[4].In addition to biological activities they are used as additives to food and cosmetics[5] and optical brightening agents[6]. Hydroxycoumarins are typical phenolic compounds and therefore, act as potent metal chelators and also free radical scavengers[7]. They are powerful chain-breaking antioxidants. The very long association of plant coumarins with various animal species and other organisms throughout evolution may account for the extraordinary range of biochemical and pharmacological activities of these chemicals in mammalian and other biological systems[8]. The coumarins are extremely variable in structure, due to the varioustypes of substitutions in their basic structure, which can influence their biological activity. The interesting biological activities of the coumarins have made them attractive targets in organic synthesis.

MATERIALS AND METHODS:

All the chemicals and solvents used in synthesis were purchased from the Himedia, Nice and Merck. The progress of reaction and purity of the synthesized compounds were checked by thin layer chromatography (TLC) with silica gel plates. The melting points were determined by a capillary method using Thermoscientific melting point apparatus and found to be uncorrected. The FT-IR spectra (nujol) were recorded on Shimadzu FT-IR spectrophotometer. The 1H NMR spectra were recorded (in DMSO) on a BRUKER AVANCE-400 (400 MHZ) spectrometer using TMS as an internal standard.

SYNTHETIC PROCEDURE:

STEP1: Synthesis of 7- hydroxyl-4-methyl coumarin

7- Hydroxy – 4-methyl coumarin was prepared by pechmann condensation.0.01moles of resorcinol and 0.01moles of ethylacetoacetate (EAA) were mixed to get a homogenous solution. To this solution 10ml of conc sulphuric acid was added and heat on water bath for 15 min, then poured with vigorous stirring into mixture of ice and water .The precipitate was filtered off and washed with water. Drying under reduced pressure was carried out to afford the crude solid. The product was recrystallized from aqueous ethanol and confirmed by thin layer chromatography and melting point.

STEP-2: Synthesis of coumarin Schiff bases

Coumarin Schiff bases were preceded by dissolving 0.002moles of step 1 product and 0.04 moles of different aromatic amines in alcohol. The reaction mixture was kept in microwave for 2minutes, then the reaction mixture was added to crushed ice with continuous stirring and then filtered, dried and product recrystallized from alcohol. The purity of the product was confirmed by thin layer chromatography and melting point. The procedure was illustrated under the scheme. Compound 1: (2E)-4-methyl-2-[(pyridine-4-yl)imino]-2h chromen-7-ol amine:Molecular weight: 252.27, Melting point: 266^0C, %yield: 25.1%,IR Data: FTIR (γ max, cm-1)2909 (=*C-H* stretch), 1384 (=*C-H* bend), 1594 (-C=C), 3364 (-OH stretch), 1384(-C-O),1594 (-C=N).^{1}H NMR (400MHZ, DMSO): δ 10.522(s, *J*1.00 N=CH), δ7.601, 7.579 (CH=C), δ 6.818, 6.813,6.797, 6.791, 6.709, 6.704, 6.125 (d, *J* 0.12, m, *J* 2.44Ar –H), δ 43.365(s, *J* 2.00 C-OH) δ 2.365, (C-NH). ^{13}CNMR (400MHZ, DMSO): δ 102.4 , 110.24, 112.83,113.12 (Ar-C), δ 126.65,126,48 (C=N), δ 154.8, 153.4 (C-OH), δ 102.21 (C=C). **COMPOUND 2:** (2E)-4-methyl-2-[(pyrimidin-2-yl)imino]-2H-chromen-7-ol amine: Molecular weight: 253.26,Melting point: 292^0C, %yield: 27%IR Data: FTIR (γ max, cm-1),

3084 (=*C-H* stretch), 1336 (=*C-H* bend), 1591 (-C=C), 3393 (-OH stretch), 1154(-C-O), 2996(0-H) **Compound 3:** N-(2E)-7-hydroxy-4-methyl-2H-chromen-2-ylidene] benzamide: Molecular weight: 323.34,Melting point: 211.3^{0}C,%yield: 20.6%,IR Data: FTIR (γ max, cm-1) 3083 (=*C-H* stretch), 1021 (=*C-H* bend), 1602 (-C=C), 3300 (-OH stretch), 1190(-C-O),1798(C=O). **Compound 4** : (2E)-4-methyl-2-(phenyl imino)-2H-chromen-7-ol:Molecular weight: 251.28,Melting point: 216.7^{0}C, %yield: 41%,IR Data: FTIR (γ max, cm-1) 3164 (=*C-H* stretch), 989 (=*C-H* bend), 1613 (-C=C), 3361 (-OH stretch), 1113(-C-O), 3500(O-H phenolic group). **Compound 5:** 4-{[(2E)-7 hydroxy-4-methyl-2H-chromen-2-ylidene]amino}benzene-1-sulfanamide: Molecular weight: 330.36,Melting point: 273.1^{0}C, %yield: 77.3%,IR Data: FTIR (γ max, cm-1)1521 , 3164 (=*C-H* stretch), 989 (=*C-H* bend), 2318 (-SH), 1613 (-C=C), 3361 (-OH stretch), 1113(-C-O),1045(S=O). **Compound 6:** (2E)-2-[(4-hydroxy phenyl)imino]-4-methyl-2H-chromen-7-ol: Molecular weight: 267.28,Melting point: 284.2^{0}C, %yield: 48.5%,IR Data: FTIR (γ max, cm-1), 3164 (=*C-H* stretch), 989 (=*C-H* bend), 2318 (-SH), 1613 (-C=C), 3361 (-OH stretch), 1113(-C-O). **Compound 7:** (2E)-2[(4-methoxy phenyl)imino]-4-methyl-2H-chromen-7-ol: Molecular weight: 281.31,Melting point: 225.7^{0}C, %yield: 28.9%,IR Data: FTIR (γ max, cm-1) 3164 (=*C-H* stretch), 989 (=*C-H* bend), 1613 (-C=C), 3361 (-OH stretch), 1113(-C-O). **Compound 8:** N-[7-hydroxy-4-methyl-2H-chromen-2-yl]-N-phenyl acetamide: Molecular weight: 267.28,Melting point: 284.2^{0}C, %yield: 24.9%,IR Data: FTIR (γ max, cm-1), 3164 (=*C-H* stretch), 989 (=*C-H* bend), , 1613 (-C=C), , 3361 (-OH stretch), 1113(-C-O),1720(C=O). ^{1}H NMR (400MHZ, DMSO): *δ* 9.903(s, *J*1.00 N=CH), *δ*6.136, 6.710, 6.716,6.797, 6.803, 6.819,6.825 (CH=C), *δ* 7.264,7.285, 7.303,7.562,7.581,7.590,7.612 (d, *J* 0.12, m, *J* 2.44Ar –H), *δ* 3.339 (s, *J* 2.00 C-OH) *δ*2.373, 2.499, 2.509,2.518 (C-NH). ^{13}CNMR (400MHZ, DMSO): *δ* 160.25, 161.13, 168.21, 102.09, 102.27, 102.22 (Ar-C), *δ* 126.51, 126.68, 128.49, 128.72 (C=N), *δ* 119.02, 118.85 (C-OH), *δ* 23.97, 18.05 (-C=C). **Compound 9:** (2E)-2-{[4-(dihydroxyamino)phenyl]imino}-4-methyl-2H-chromen-7-ol: Molecular weight: 298.29,Melting point: 265.9^{0}C, %yield: 33.6%,IR Data: FTIR (γ max, cm-1) 3148 (=*C-H* stretch), 835 (=*C-H* bend), 1584 (-C=C), 3287 (-OH stretch), 1271(-C-O),1441(C-N). ^{1}H NMR (400MHZ, DMSO): *δ* 8.640(s, *J*1.00 N=CH), *δ*7.381, 7.192 (CH=C), *δ* 7.987, 7.970, 7.966, 7.822, 7.805, 7.789, 7.786, 7.668, 7.650 (d, *J* 0.12, m, *J* 2.44Ar –H), *δ* 4.497 (s, *J* 2.00 C-OH) *δ*2.515, 2.510, (C-NH).^{13}CNMR(400MHZ, DMSO): *δ* 130.26, 128.66, 127.59, 126.77, 125.05, 124.14, 119.30, 115.96, 114.83 (Ar-C), *δ* 157.87 (C=N), *δ* 150.24 (C-OH), *δ* 123.3, 129.5 (C=C). **Compound 10:** (2E)-2[(4-chloro phenyl)imino]-4-methyl-2H-chromen-7-ol: Molecular weight: 285.72, Melting point: 230.5^{0}C, %yield: 16.3%,IR Data: FTIR (γ max, cm-1), 3147 (=*C-H* stretch), 812 (=*C-H* bend), 1793 (-C=C), , 3147 (-OH stretch), 1069(-C-O),663(C-Cl). **Compound 11:** (2E)-4-methyl-2-[2-phenyl hydrazine-1-ylidene]-2H-chromen-7-ol: Molecular weight: 266.29,Melting point: 219.3^{0}C, %yield: 17.5%,IR Data: FTIR (γ max, cm-1), 3247 (=*C-H* stretch), 950 (=*C-H* bend), 1606 (-C=C), 1555(-NH 2^0 amine stretch), 3247 (-OH stretch), 1270(-C-O). ^{1}H NMR (400MHZ, DMSO): *δ* 8.640(s, *J*1.00 N=CH), *δ*7.381, 7.192 (CH=C), *δ* 7.987, 7.970, 7.966, 7.822, 7.805, 7.789, 7.786, 7.668, 7.650 (d, *J* 0.12, m, *J* 2.44Ar –H), *δ*4.497 (s, *J* 2.00 C-OH) *δ*2.515, 2.510, (C-NH). ^{13}CNMR (400MHZ, DMSO): *δ* 130.26, 128.66, 127.59, 126.77, 125.05, 124.14, 119.30, 115.96, 114.83 (Ar-C), *δ* 157.87 (C=N), *δ* 150.24 (C-OH), *δ* 123.3, 129.5 (C=C). **Compound 12:** 4-{[(2E)-7hydroxy-4-methyl-2H-chromen-2-ylidene]amino}benzoic acid: Molecular weight: 295.29,Melting point: 287.4^{0}C,

%yield: 21.4%,IR Data: FTIR (γ max, cm-1) 3164 (=*C-H* stretch), 989 (=*C-H* bend), 1613 (-C=C), 3361 (-OH stretch), 1113(-C-O),1604(C=O). **Compound 13**: 6-{[(2E)-7hydroxy-4-methyl-2H-chromen-2-ylidene]amino}-1,3-diazinane-2,4-dione: Molecular weight: 285.25,Melting point: 264.2^{0}C, %yield: 32.5%,IR Data: FTIR (γ max, cm-1) 3164 (=*C-H* stretch), 989 (=*C-H* bend),1514(R_2-NH 2^0 amine)1613 (-C=C), 3361 (-OH stretch), 1113(-C-O). **Compound 14**: (2E)-2{[2-amino-1-(naphthalene-1-yl) ethyl]imino}-4-methyl-2H-chromen-7-ol: Molecular weight: 344.41,Melting point: 217.8^{0}C, %yield: 51%. IR Data: FTIR (γ max, cm-1) 3164 (=*C-H* stretch), 989 (=*C-H* bend),, 1613 (-C=C), 3445 (-$NH_2 1^0$ amine stretch), 3361 (-OH stretch), 1113(-C-O).

ANTIBACTERIAL ACTIVITY[9]

All the synthesized compounds were examined for invitro antibacterial activity against an assortment of two gram-positive bacteria *Staphylococcus aureusNCIM 2901* and *Bacillus subtilis MTCC 441* and two Gram-negative bacteria *Escherichia coliNCIM 2563* and *Proteus vulgaris MTCC 1771* by diffusion method. Tetracycline and Chloramphenicol were used as an internal standard.

EXPERIMENTAL PROCEDURE:

Nutrient agar (High media) was dissolved and distributed in 25ml quantities in an boiling tubes and were sterilized in an autoclave at 121^{0}C (15LBS/52.in) for 20minuts. The medium was inoculated at one percent level using 18 hrs old cultures of the test organism mentioned above aseptically into sterile petridishes and allowed to set at room temperature for above 30min. In a size of 4 inches petridishes, five cups of 8mm diameter at equal distance were made in each plate. In the cups the test solutions of different concentrations were added and in another plate cups were made for standard and control. The plates thus prepared were left for 90 minutes in a refrigerator for diffusion. After incubation for 24 hours at 37^{0}C the plates were examined for inhibition zones. The experiment was performed in duplicate and the average diameter of the zones of inhibition measured and recorded in table1.

ANTIFUNGAL ACTIVITY [10]:

The antifungal activity of the compounds was assayed against four different strains of *Aspergillus niger MTCC 282, Penicillium chrysogenum MTCC5108 and Penicillium notatum NCIM 742*. Potato dextrose agar (Hi-media) was dissolved and distributed in 25 ml quantities in 100ml conical flasks and were sterilized in an autoclave at 121^{0}C (15lbs/sq.in) for 20 minutes. The medium was inoculated at one percent level using 18hr old cultures of organisms mentioned above aseptically in to sterile petridish and allowed to set at room temperature for about 30 minutes. . In a size of 4 inches petridish 5 cups of 8mm diameter at equal distance were made in Petri plate with a sterile borer. The solutions of test and standard at concentrations (250µg/ml, 200µg/ml, 150µg/ml, 100µg/ml and 50µg/ml) were added to respective cup aseptically and labelled accordingly. DMF as control did not show any inhibition. The plates were left for 90 minutes in refrigerator for diffusion. After incubation for 24 hrs at 37^0 ± 1^{0}c. The plates were examined for incubation inhibition zones. The experiments were performed in duplicate and the average diameters of the zones of inhibition were summarized in **Table 2.**

RESULTS AND DISCUSSION:

All the compounds (1-14) were tested for anti bacterialactivity against an assortment of two gram positive bacteria*Staphylococcus aureus NCIM 2901, Bacillus subtilis MTCC441* and two gram-negative bacteria *Pseudomonas aeruginosa,Proteus vulgaris MTCC 1771.*

Table 1: Anti bacterial activity

Zone of inhibition(Diameter in cm)																
Compound	**E-coli**				**Staphylococcus aureus**				**Pseudomonas aeruginosa**				**Proteus vulgaris**			
	100 µ/ml	150 µ/ml	200 µ/ml	250 µ/ml	100 µ/ml	150 µ/ml	200 µ/ml	250 µ/ml	100 µ/ml	150 µ/ml	200 µ/ml	250 µ/ml	100 µ/ml	150 µ/ml	200 µ/ml	250 µ/ml
1	0.9	1.5	1.3	2	0.9	1.5	1.3	1.4	0.9	1.1	1.2	1.3	1.1	1.2	1.2	1.3
2	1.3	1.3	1.4	1.5	1.1	1.3	1.3	1.5	1.1	1.1	1.2	1.3	1.1	1.2	12	1.4
3	1.2	1.3	2	1.5	1.1	1.2	1.2	1.2	1	1.1	1.2	1.3	1	1.1	1.1	1.2
4	1	1.1	1.2	1.2	1.1	1.2	1.2	1.3	0.9	1	1.1	1.1	1.2	1.1	1.3	1.1
5	1	1.1	1.1	1.1	1.1	1.1	1.2	1.2	0.9	1.1	1.1	1.2	1.1	1.2	1.4	1.3
6	1.3	1.4	1.5	1.5	1.2	1.5	1.2	1.3	1.1	1.2	1.2	1.3	1	1.1	1.1	1.2
7	1.2	1.2	1.3	1.3	1.1	0.9	1.1	1.2	1.1	1.2	1.4	1.4	0.9	1	1.1	1.2
8	1.1	1.2	1.2	1.3	1	1.1	1.2	1.3	1.1	1.2	1.3	1.5	1.1	1.2	1.2	1.3
9	1.1	1.1	1.2	1.2	1.1	1.2	1.3	1.3	1.2	1.4	1.4	1.5	1.1	1.2	1.3	1.4
10	1.2	1.3	1.3	1.4	1.1	1.1	1.1	1.2	1.1	1.2	1.2	1.3	1	1.2	1.2	1.3
11	1.1	1.2	1.2	1.3	1.1	1.1	1.1	1.2	1	1.2	1.3	2	1.2	1.3	1.3	1.4
12	1.1	1.2	1.3	1.4	1.1	1.1	1.2	1.3	1.2	1.3	1.4	1.5	1	1.1	1.1	1.2
13	0.9	1	1.1	1.2	1	1.1	0.9	1.1	1	0.9	1.1	1.2	0.9	1.1	1.2	1,1
14	1.1	0.9	1	1.1	0.9	1.3	1.1	1	0.9	1	1.1	1.2	1.1	0.9	1	1.1
Tetracycline	2	2	2.1	2.2	2.1	2.2	2.3	2.3	2	2.1	2.1	2.2	2	2.1	2.2	2.3
Chloramphenicol	2.1	2.2	2.3	2.4	2	2.1	2.2	2.3	2.1	2.2	2.3	2.4	2	2.1	2.2	2.3

TABLE 2: Anti Fungal activity

Compound	Aspergilus niger				Pencillium chrysogenum				Pencillium notatum			
	100 µ/ml	150 µ/ml	200 µ/ml	250 µ/ml	100 µ/ml	150 µ/ml	200 µ/ml	250 µ/ml	100 µ/ml	150 µ/ml	200 µ/ml	250 µ/ml
1	0.8	0.9	1	1.1	1	1.2	1.8	1.9	1.5	1.6	1.7	2
2	0.9	1.1	1.2	1.3	0.9	1	1.1	1.2	1.1	1.2	1.3	1.4
3	0.9	1	1.1	1.2	0.8	0.9	1	1.1	0.9	1.1	1.3	1.4
4	0.9	1	1.1	1.2	1	1.1	1.2	1.3	1.1	1.2	1.3	1.4
5	0.9	1	1.2	1.3	1.2	1.5	1.6	1.8	0.9	1	1.5	1.6
6	0.8	0.9	1	1.1	1	1.1	1.2	1.3	1.1	1.2	1.3	1.4
7	0.8	0.8	1	1.1	1.1	1.2	1.3	1.4	1.2	1.3	1.4	1.5
8	0.8	0.9	1.1	1.2	0.9	1.5	1.6	1.8	0.9	0.9	1	1.1
9	0.9	1	1.2	1.3	0.8	1	1.5	2	1.2	1.3	1.4	2
10	0.7	0.8	1	1.1	1.2	1.5	1.7	2	1.2	1.3	1.5	1.7
11	0.8	0.9	1	1.1	1	1.2	1.8	1.9	1.5	1.6	1.7	2
12	0.7	0.9	1	1.1	0.9	1.1	1.3	1.5	1.3	1.5	1.7	1.9
13	0.9	1	1.5	1.3	0.9	1.1	1.2	1.4	1.1	1.3	1.4	1.1
14	1	1.1	2	1.6	1.5	1.1	1.3	1.5	1.8	0.9	1.1	1
Fluconazole	1.6	1.7	1.8	1.9	1.7	1.8	1.9	2	1.8	1.9	2	2.1

Tetracycline and Chloramphenicol were used as standards. Of all the derivatives synthesized compounds 1, 2, 6, 8, 12exhibited good antibacterial activity. The results of the compounds represented in Table2 showed a wide range of anti-fungal activity. Compounds 1, 11, 12, and 14were found to exhibit the most potent *in vitro* anti-fungal activity against *Pencillium notatum NCIM 742*, *Pencillium chrysogenum MTCC5108and* found to be equally potent with that of standard Fluconazole.

CONCLUSION

Coumarin Schiff bases were synthesized by microwave method. The structures of the compounds are characterised by IR and ^{1}H and ^{13}C NMR spectral data.

Anti-bacterial and anti-fungal *in-vitro* studies were carried out for synthesised compounds. Among 14 compounds synthesised 1, 2, 6, 8, 11, 14, 12were active against both gram-positive organisms and gram negative organisms. The structure-activity relationship studies based on the above *in vitro* results clearly indicate that compounds with electron donating groups on the aromatic ring showed increased potency. The intense activity of the compounds is also greatly influenced by the amount of activation or deactivation and position of the groups on the ring. The findings of the study inferred the design and that the functioning of synthesised compounds as antibacterial, anti fungal activities rendering them as lead molecules for further development of newer agents with greater efficacy and safety.

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Fig 1: Anti bacterial Activity

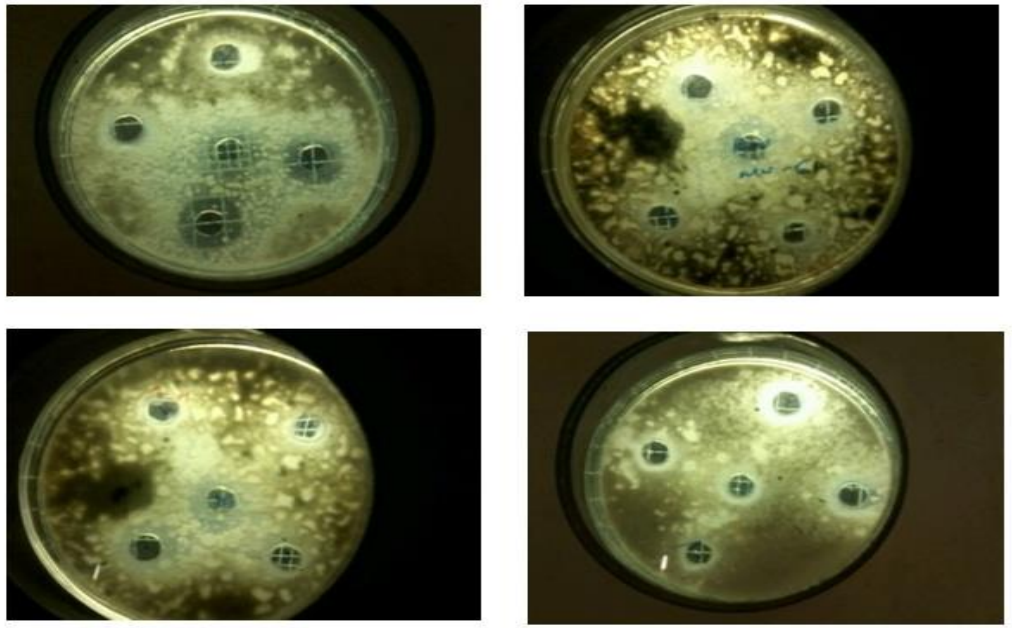
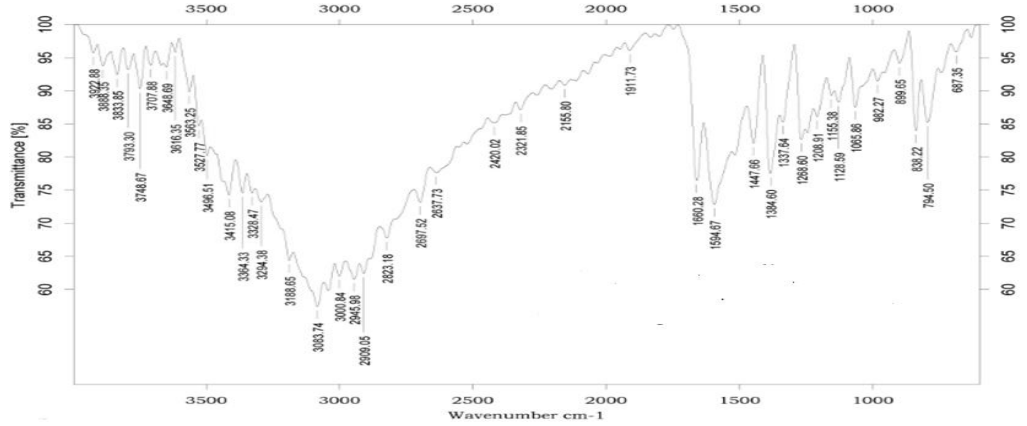
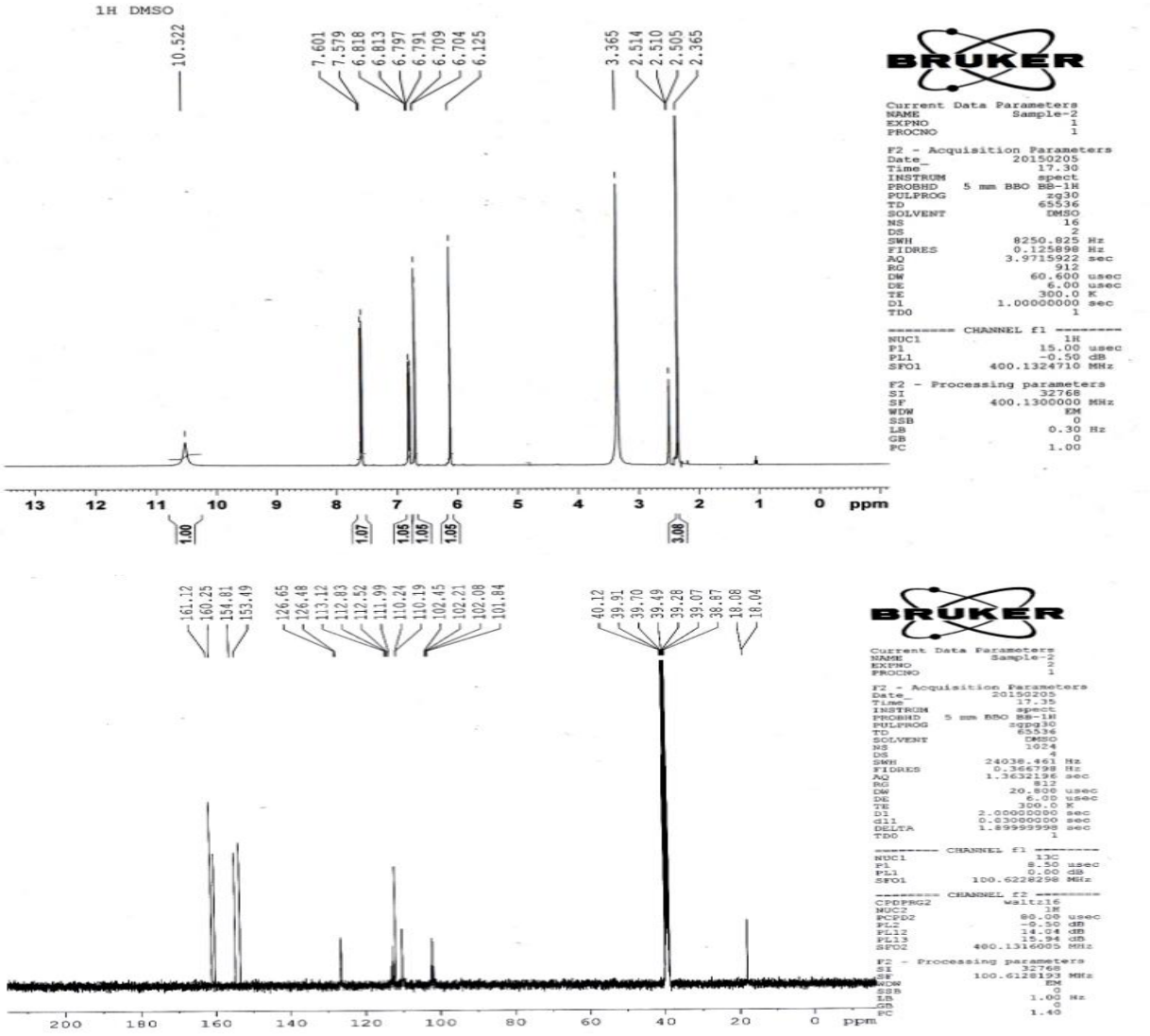
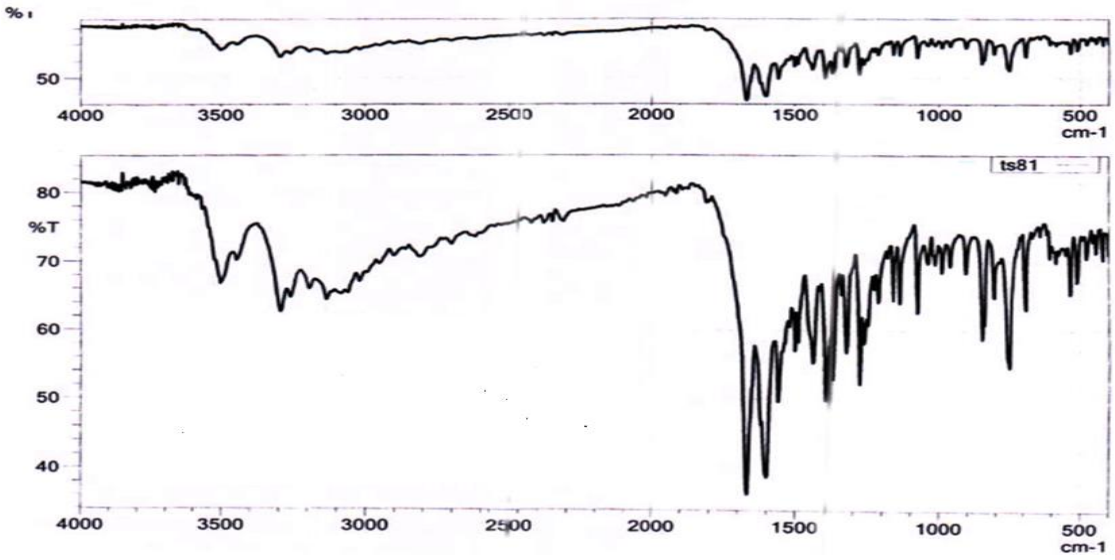


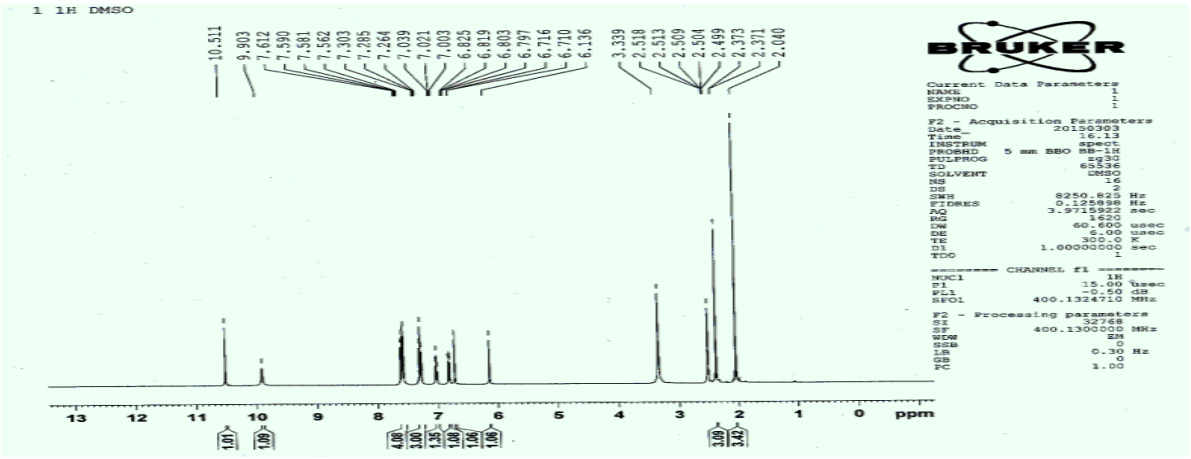
Fig 2: Anti fungal Activity

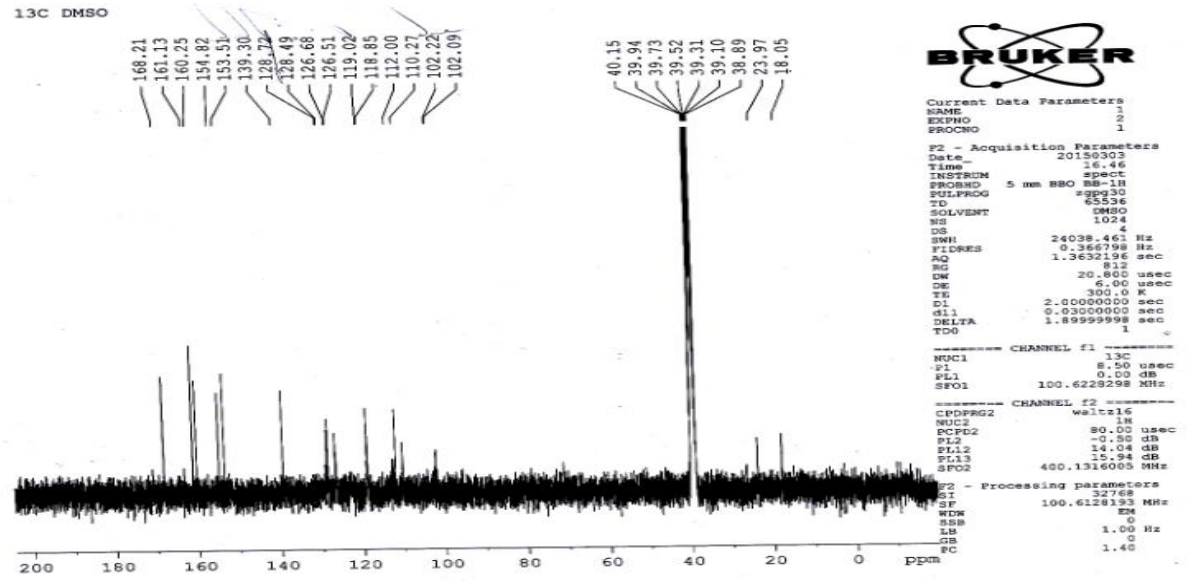




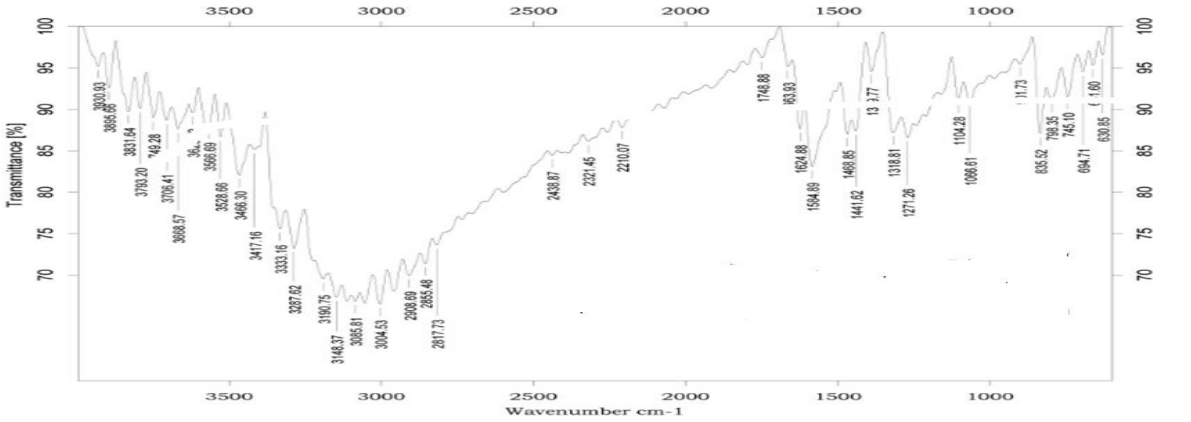
IR,H[1] &C[13] NMR OF COMPOUND-1

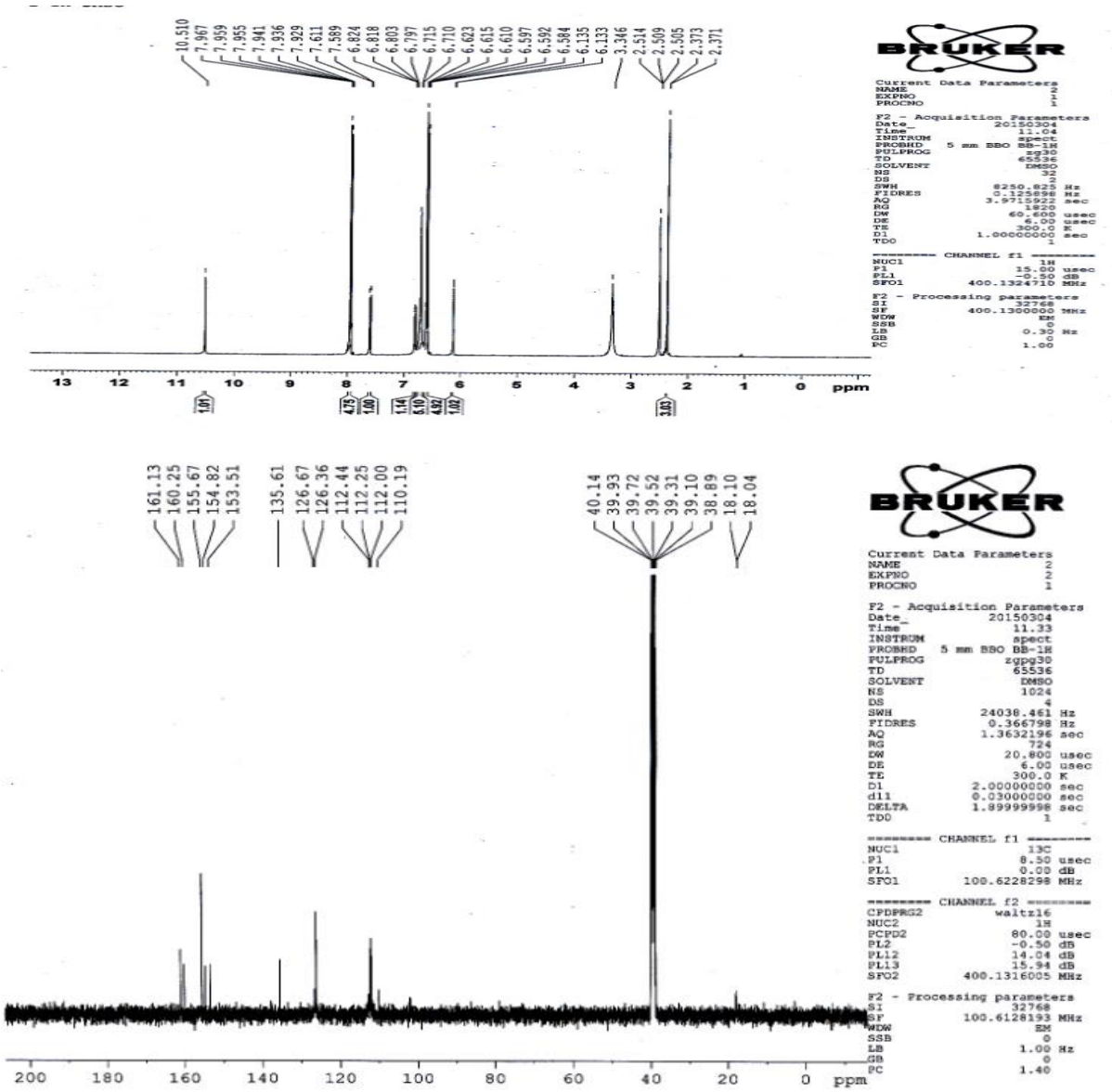




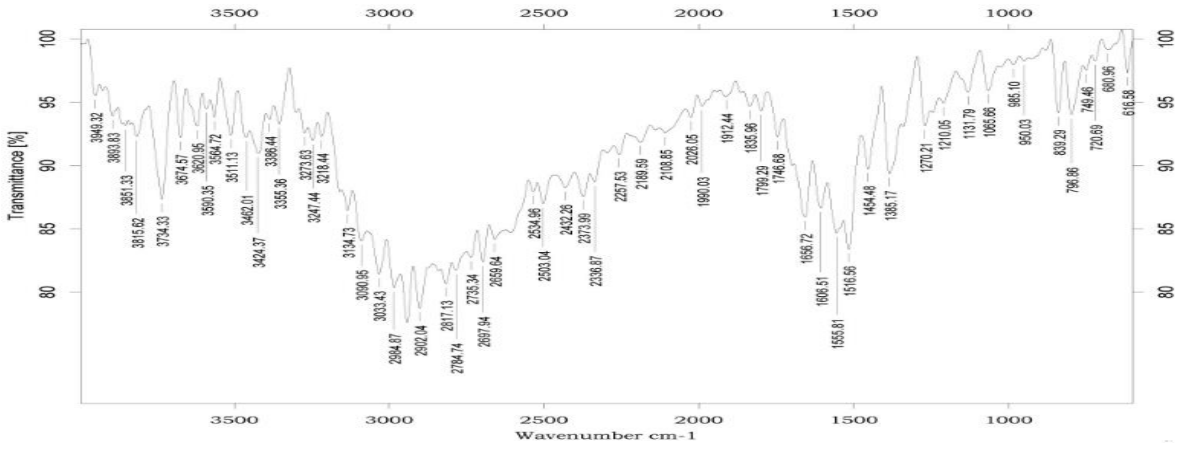


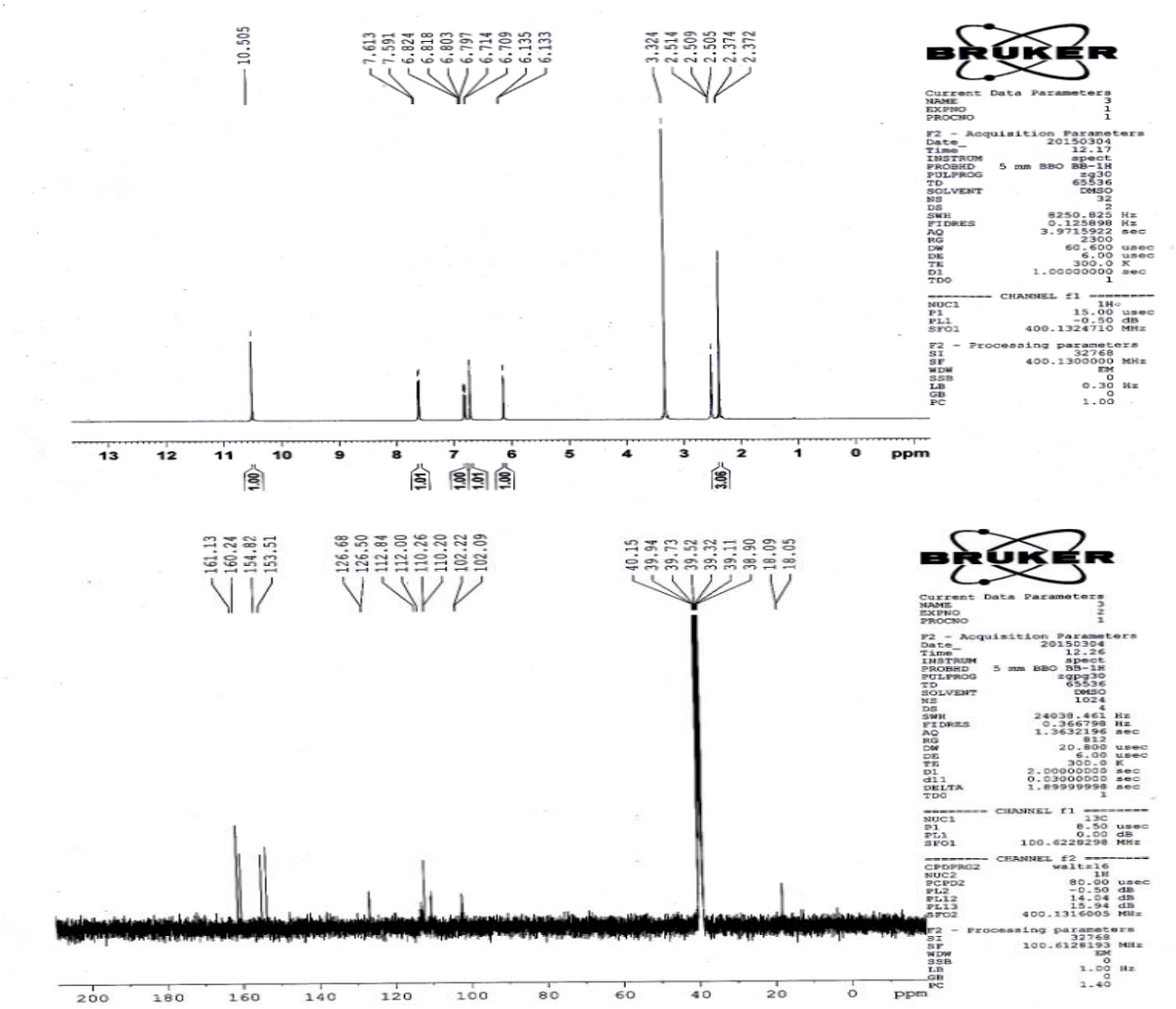
IR,H[1] &C[13] NMR OF COMPOUND-8





IR,H^{1} &C^{13} NMR OF COMPOUND-9





IR,H^1 &C^{13} NMR OF COMPOUND-11

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