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Synthesis and identification of some quinazolines and 1,3-oxazepines derived from thiosemicarbazone and evaluation of its bacterial activity

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Abstract : *Thiosemicarbazide derivatives (A1-A2) were synthesized by the reaction of (p-bromo aniline and p-amino acetophenone) respectively withcarbondisulfide (CS2) / hydrazine hydrate .Compounds (A1-A2) were allowed to react with aromatic benzaldehyde (p-N,N-dimethyl amino , p-chloro and p-hydroxybenzaldehyde) to form compounds of thiosemicarbazone (A3-A8) using fusion method.Quinazoline compounds (A9-A14) were also formed by reaction of (A3-A8) with anthranilic acid using fusion method . Compounds (A3-A8) were also reacted with maleic anhydride to form 1,3- oxazepine compounds (A15-A20) by fusion method. The prepaered compounds were identified by (I.R ,1H.NMR, 13C.NMR and melting points.) .*

Keywords : *Thiosemicarbazide , thiosemicarbazone, quinazoline , 1,3- oxazepine.*

INTRODUCTION

Thiosemicarbazide compounds have been formed by the reaction of aromatic amine (p- methoxy aniline) and carbondisulfide / hydrazine hydrate (1).Thiosemicarbazone compounds have been formed via the reaction of thiosemicarbazide with different aromatic aldehydes in many ways such such as refluxe and fusion and microwave (2-6) p-chlorobenzaldehyde reacted with 2-hydrazino benzothiazole (7) . microwave technique was used to form thiosemicarbazone via the reaction of furfural and isoniazide (8) . These compounds have a biological activity towards malaria ,germs,fungi,viruces and cancer (9-14).Quinazoline compounds have been preapered in many ways especially the reaction of thiosemicarbazone with anthranilic acid (15).Uracil compounds having azomethene group , were reacted with anthranilic acid to form these heterocyclic compounds in high yield (16) 1,3- oxazepines

compounds were also formed using reaction of shiff bases and maleic anhydride (17-18). A substituted naphthalinewith azomethene group was reacted with maleic anhydride to prepare such heterocyclic compounds (19). High yield of such compounds were obtained through fusion method (6) , and used in medicinal applications (20). We intended to use fusion method in forming new quinazolines and 1,3-oxazepines compounds using new thiosemicarbazones as starting material to extend the work in this field.

Experimental part

Instruments and chemical materials:

Melting points were measured byelectrother 9300 apparatus and are not

corrected. FTIR spectra were recorded by FT-IR.470 Shimadzu infrared spectrophotometer .^{1}H.NMR and^{13}C.NMR spectra were measured by ultrashield 400 MHz spectrophotometer in Turkey , university of soljok. Dept. of chemisty and using (DMSO-d6) .

All chemical materials used , were supplied from merck and fluka company , and used without purification.

Synthetic part :

Synthesis of thiosemicarbazides(A_1-A_2) (1)

In 20 ml of ethanol , 0.01 mole of substituted aromatic amine was dissolved, then 20 ml of carbondisulfide wad added in 15 minutes with stirring .The mixture was left for 1h , then it was added to 20 ml of hydrazine hydrate . The mixture cooled and poured in water / ice , the solid precipitated filtered , washed with water and recrystallized of ethanol .

Synthesis of thiosemicarbazones(A_3-A_8) (21)

0.01 mole of compounds (A_1-A_2) was mixed with 0.01 mole of substituted aromatic aldehydes in a pyrex container without using a solvent , the mixture was gently heated for 15 minutes with stirring until changing in the colour and shape , the crude material was collected and recrystallized of ethanol.

Synthesis of quinazolines(A_9-A_{14}) (22)

0.01 mole of compounds (A_3-A_8) was mixed with 0.01mole of anthranilic acid in a pyrex container without using a solvent , the mixture was gently heated for 15 minutes with stirring until changing in the colour and shape , the crude material was collected and recrystallized of ethanol.

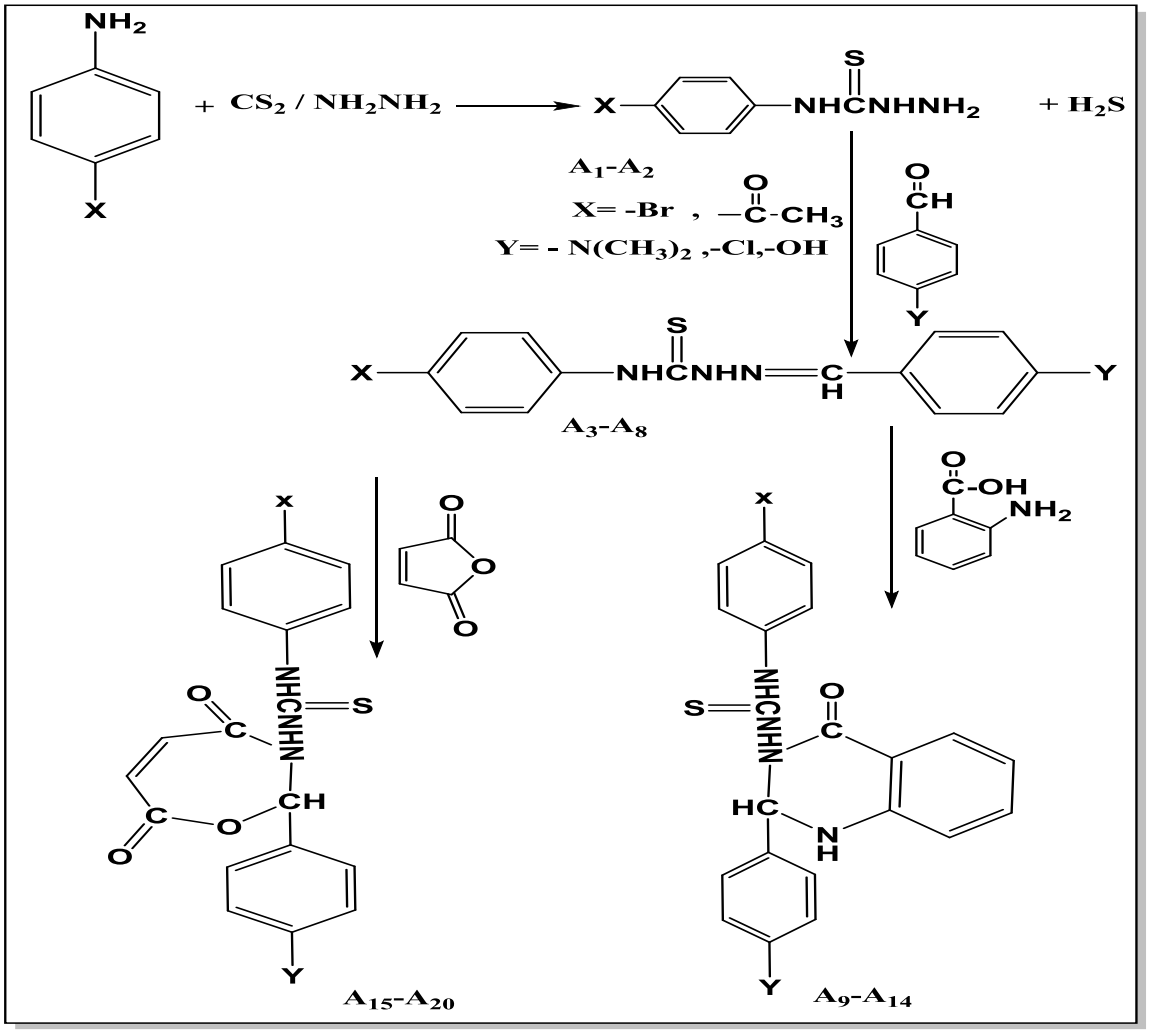
Synthesis of 1,3- oxazepines (A_{15} –A_{20}) (22)

0.01 mole of compounds (A_3-A_8) was mixed with 0.01mole of maleic anhydride in a pyrex container without using a solvent , the mixture was gently heated for 15 minutes with stirring until changing in the colour and shape , the crude material was collected and recrystallized with ethanol.

Table 1: physical properties of synthesized compounds

Compound no.	X	Y	Coulor	M.P	Yield
A1	-Br	-	brown	120-122	83
A2	$-COCH_3$	-	yellow	166-168	80
A3	-Br	$-N(CH_3)_2$	orange	170-172	88
A4	-Br	-Cl	yellow	141-143	82
A5	-Br	-OH	Red	138-140	84
A6	$-COCH_3$	$-N(CH_3)_2$	yellow	173-175	81
A7	$-COCH_3$	-Cl	brown	131-133	85
A8	$-COCH_3$	-OH	Red	137-139	84
A9	-Br	$-N(CH_3)_2$	Pink	108-110	83
A10	-Br	-Cl	brown	164-166	82
A11	-Br	-OH	yellow	139-141	85
A12	$-COCH_3$	$-N(CH_3)_2$	Red	191-193	80
A13	$-COCH_3$	-Cl	Pink	159-161	84
A14	$-COCH_3$	-OH	brown	128-130	81
A15	-Br	$-N(CH_3)_2$	Red	143-145	83
A16	-Br	-Cl	yellow	167-169	86
A17	-Br	-OH	Pink	125-127	84
A18	$-COCH_3$	$-N(CH_3)_2$	brown	144-146	82
A19	$-COCH_3$	-Cl	yellow	105-107	80
A20	$-COCH_3$	-OH	brown	183-185	83

Fig 1: Diagram for the prepeared compounds

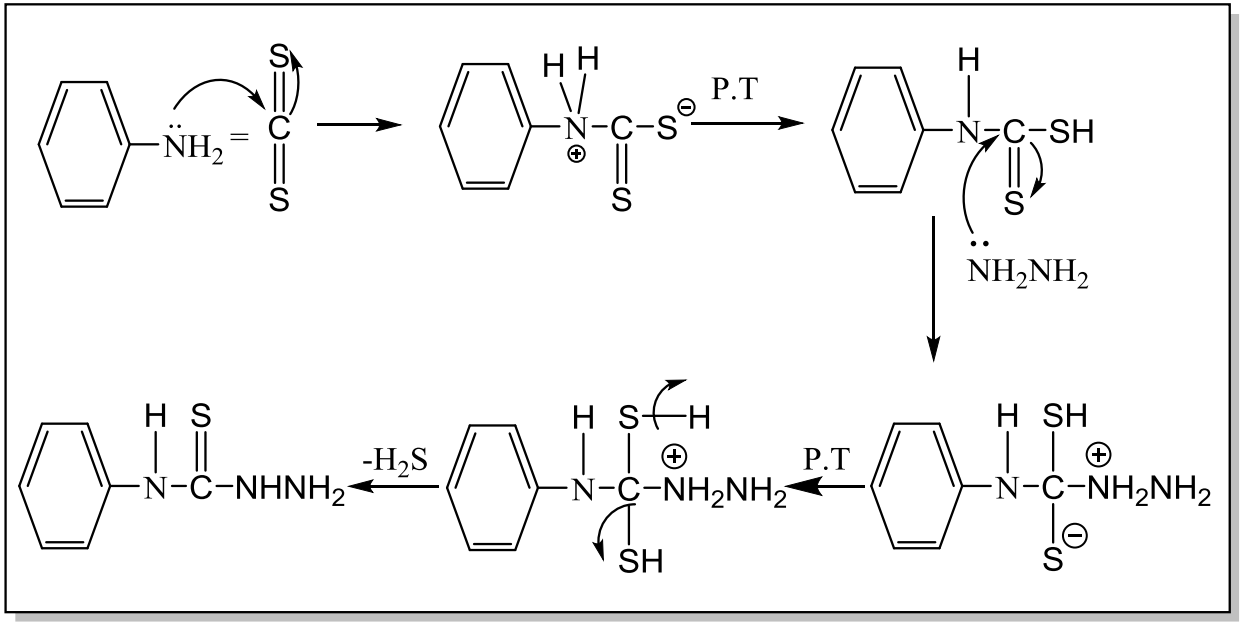


Bacterial activity evaluation part :

This part included applying the synthesized compounds on two types of bacteria which were (gr – pseudomonas aeruginosa and gr + staphylo- coccusaureus) , the concentrations of compounds were (0.0001 , 0.001 ,0.01) mg/ml , using DMSO as a solvent . The sensitivity of bacteria against these compounds , was tested according to agar – well diffusion method (23) and the obtained results were compared with control group (amoxilline , ampicilline and ciprofloxacine) .

Results and discussion :(A_1- A_2)

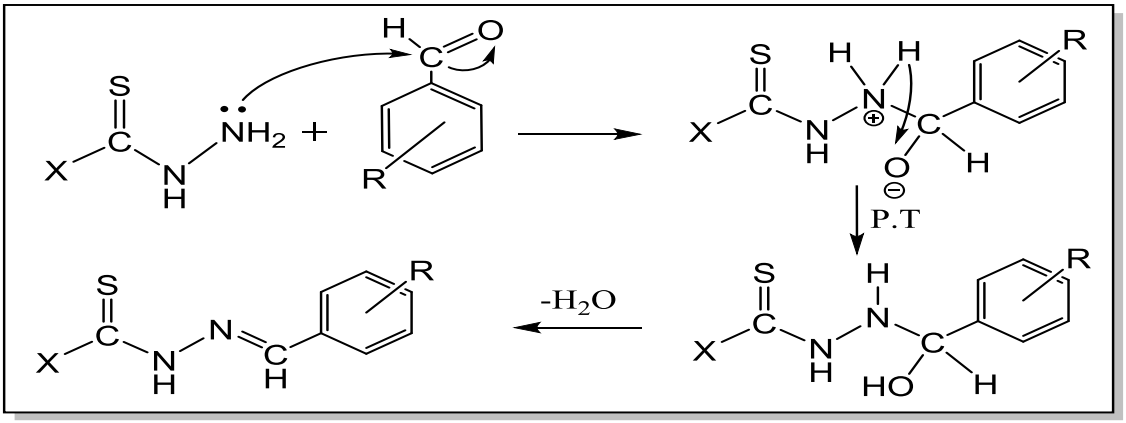
Thiosemicarbazide derivatives (A_1,A_2) were synthesized via the reaction of aromatic amine (p- bromo aniline and p- amino acetophenone) , respectively with carbondisulfide in presence of hydrazine hydrate , as in mechanism shown below (24)



IR spectrum data in table (2) show appearing of (NH_2) peak at (3259-3475) cm-1 , (NH) peak at (3136-3230) cm-1 and (C=S) peak at (1124-1126) . H.N.M.R. of compound (A1) show the following signals at ppm using d-DMSO as solvent : (8.73 NH) , (5.00 NH_2) (7.09 -7.74 Ar-H).

Compounds(A_3 – A_8)

Hydrazones compounds were synthesized via the reaction of aromatic aldehyde with thiosemicarbazide compounds as in mechanism shown below(24)



IR spectrum data in table (3) show appearing (C=N) peak at (1600-1620)

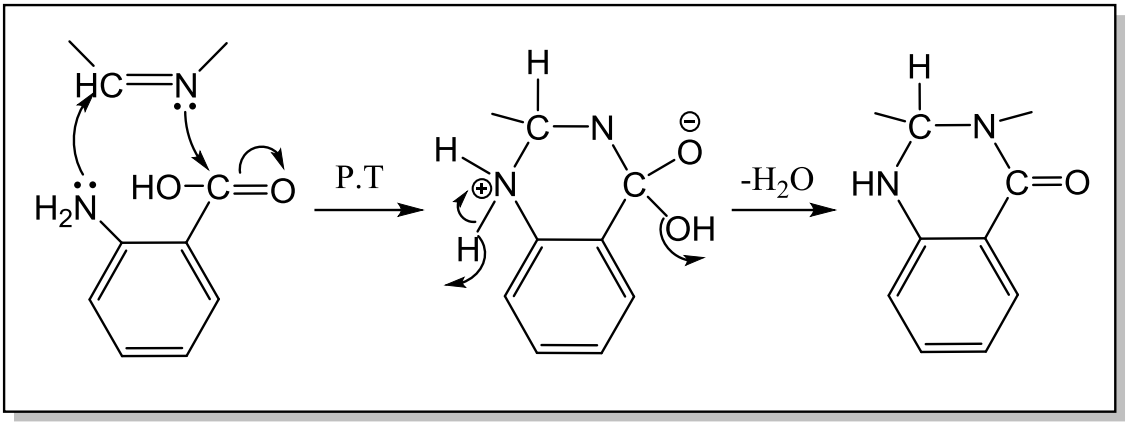
H.N.M.R of compound (A_2) show the following signals at ppm m using d- DMSO as a solvent : (11 NH) , (7.1-7.67 Ar-H) (6.69 C-H) and (3.01 $N(CH_3)_2$.

C13.N.M.R for compound (A3) show the following signals in ppm ,using d-DMSO as a solvent : (175 C=S) , (137 N=CH) and (127-135 C-Ar ring)

C13.N.M.R. ror compound (A_{13}) show the following signals in ppm , using d-DMSO as a solvent : (211 C=O) M(175 C=S) , (137 N=CH) and (81 CH3-C=O) (25)

Compounds (A_9-A_{14})

Quinazolines compounds were synthesized via the reaction of hydrazones with anthranilic acid as in the mechanism shown below (24)



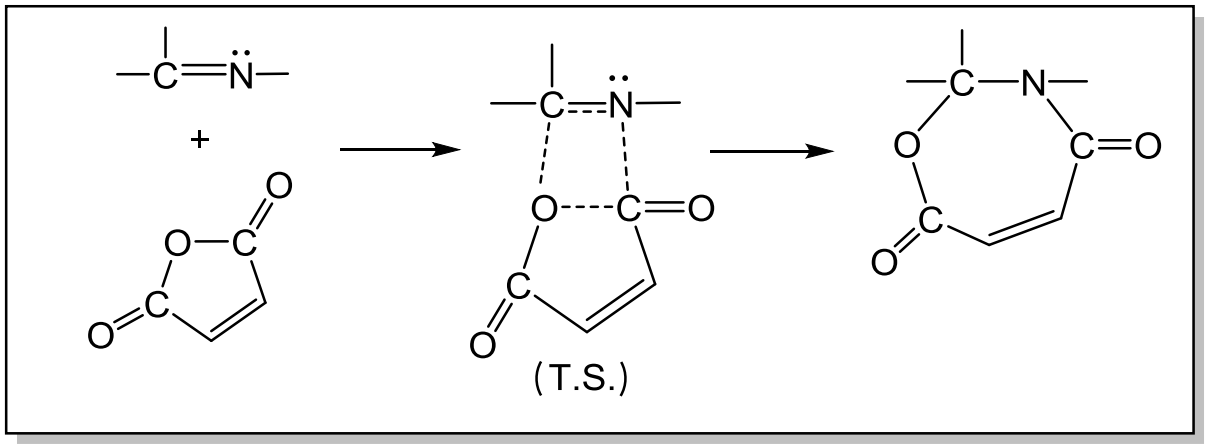
IR spectrum data in table (4) show appearing of (C-N) peak at (1232-1292) cm-1 , (C=O of the ring) at (1650-1660) cm-1.

H.N.MR . of compound (A_{19}) show the following signals , using d-DMSO as a solvent at ppm : (8.56 NH) , (7.00-7.71 Ar-H) , (3.8 CH_3) and (6.5 OH)

C13.N.M.R of compound (A_7) show the following signals ,using d-DMSO as a solvent at ppm : (175 C=S) , (160 C=O ring) and (127-135 C-Ar ring) (25)

Compounds (A_{15}-A_{20}) :

1,3- oxazepines were synthesized via the reaction of hydrazone derivatives with maleic anhydrie , as in the mechanism shown below (24)



IR spectrum data in table (5) show appearing of (C=O lactone) peak at (1712-1735) cm-1and (C=O lactam) peak at (1643-1650) cm-1.

H.N.M.R. of compound (A_8) show the following signals at ppm , using d-DMSO as a solvent : (7.9 NH) ,(7.12- 7.89 Ar-H) (4.12-5.32 CH=CH ring) .and (3.82 C-H ring)

Bacterial activity :

The bacterial activity against the synthesized compounds showed that a significant effect as inhibitors for the growth of bacteria , compared with standard antibiotic used as shown in table (6) and (7)

Table 2: IR spectrum data for thiosemicarbazide compounds in cm-1.

Compound no.	NH2	N-H	C=S	C=C ar.	C-H ar	**others**
A1	3259-3475	3230	1126	1589-1618	3030	**C-Br 937**
A_2	3263-3323	3136	1124	1560-1585	3010	**C=O1710** **C-H aliph 2965**

Table 3

IR spectrum data for hydrazones compounds in cm-1 .

Compound no.	N-H	C-H ar.	C=S	C=N	C=C ar.	C-N	**Others**
A_3	3446	3159	1174	1604	1450-1515	1224	**C-H al.2923 C-Br 945**
A_4	3377	3163	1170	1618	1564-1595	1211	**C-Br 860**
A_5	3332	3030	1164	1600	1510-1598	1234	**OH 3436 C-Br 871**
A_6	3344	3025	1173	1602	1431-1517	1228	**C=O 1715 C-H al. 2894**
A_7	3375	3112	1176	1620	1556-1595	1276	**C=O 1710**
A_8	3228	3170	1164	1610	1508-1598	1261	**C=O 1743 OH 3431**

Table 4: IR spectrum data for quinazoline in cm -1:

Compound no.	N-H	C=S	C-H ar.	C=C ar.	C-N	C=O	**Others**
A_9	3431	1147	3103	1429 - 1512	1234	1645	**C-Br 943 C-H al. 2927**

A_{10}	3481	1164	3100	1515-1598	1238	1662	**C-Cl 819** **C-Br 955**
A_{11}	3359	1166	3050	1448-1510	1236	1650	**C-Br 947** **OH 3427**
A_{12}	3425	1172	3030	1450-1523	1232	1652	**C-H al. 2912**
A_{13}	3242	1157	3015	1487-1550	1292	1660	**C-Cl 817**
A_{14}	3242	1163	3025	1438-1508	1244	1652	**OH 3448** **C-H al. 2920**

Table 5: IR spectrum data for 1,3- oxazepines compounds in cm-1:

Compound no.	N-H	C=S	C-H ar.	C=C ar.	C-N	C=O LN	C=O LM	Others
A_{15}	3166	1174	3020	1519-1598	1228	1712	1650	C-Br 941
A_{16}	3236	1197	3010	1560-1591	1274	1735	1645	C-H al.2920
A_{17}	3174	1166	3015	1466-1517	1228	1716	1643	OH 3450
A_{18}	3373	1172	3024	1519-1598	1223	1722	1648	C-H al.2980
A_{19}	3190	1191	3018	1521-1587	1232	1720	1650	C-Cl 823
A_{20}	3229	1164	3025	1442-1512	1265	1723	1647	OH 3427

Table 6: bacterial evaluation of the synthesized compounds against used bacteria (inhibition circle diameter measured in mm.)

Compound no.	Conc. Mg/ml	Pseudomonas aeruginosa	Staphylococcus aureus
A_8	0.0001	-	-
	0.001	+	-
	0.01	++	-
A_9	0.0001	-	-
	0.001	+	+
	0.01	+	++
A_{10}	0.0001	+	-
	0.001	+	-
	0.01	++	+
A_{11}	0.0001	-	-
	0.001	+	-
	0.01	+	-
A_{12}	0.0001	-	-
	0.001	+	+
	0.01	+++	+
A_{13}	0.0001	-	+
	0.001	+	+
	0.01	++	+
A_{14}	0.0001	-	-
	0.001	-	-
	0.01	+	-

A_{15}	0.0001	-	-
	0.001	+	++
	0.01	++	++
A_{16}	0.0001	-	-
	0.001	-	++
	0.01	-	++
A_{17}	0.0001	-	-
	0.001	+	+
	0.01	++	+
A_{18}	0.0001	-	-
	0.001	+	+
	0.01	++	+

(+) : inhibition in 5-15 mm , (-) : no, inhibition

(++) : inhibition in 12-25 mm , (+++) : inhibition in 25-35 mm

Table 7: the bacterial activity of antibiotic (control sample) against bacteria.

NO.	Name	Pseudomonas aeruginosa	Staphylococcus aureus
1	Amoxcilline	++	++
2	Ampicilline	++	+
3	Ciproflaxicine	+	++

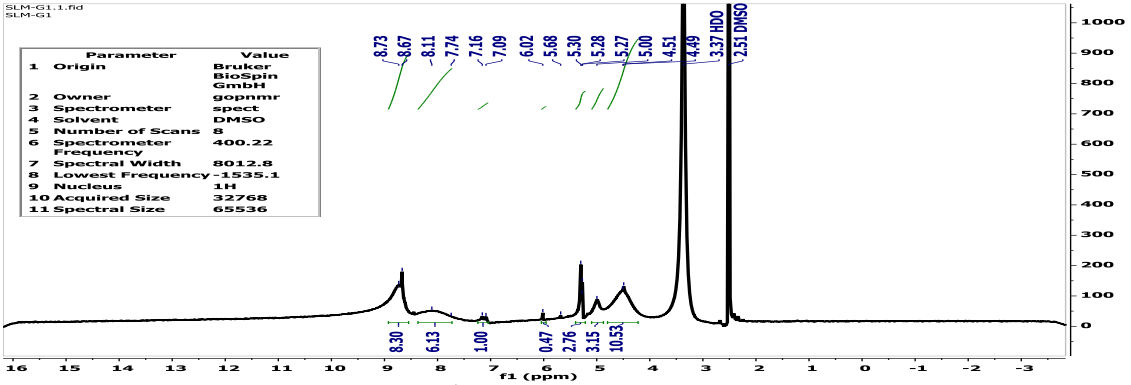


Fig1:(^{1}H.N.M.R) of compound(A_1)

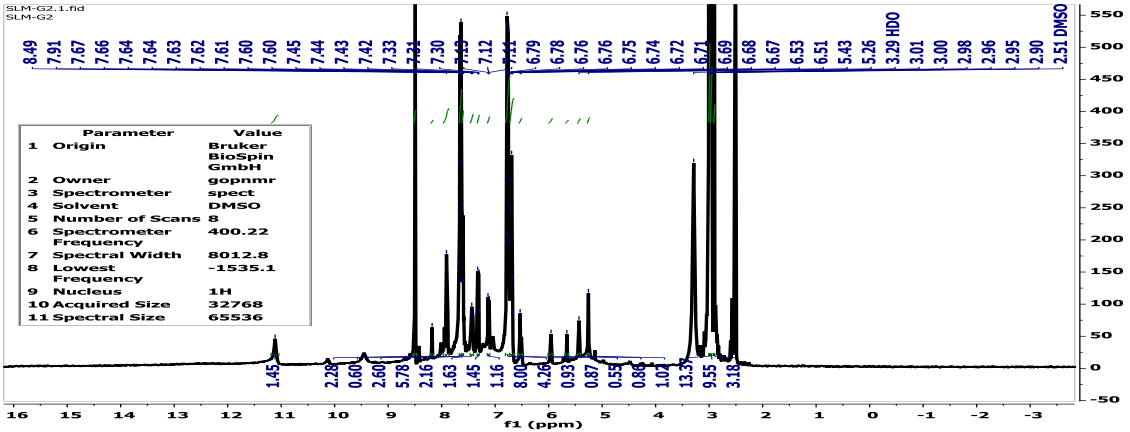


Fig2:(^{1}H.N.M.R) of compound(A_2)

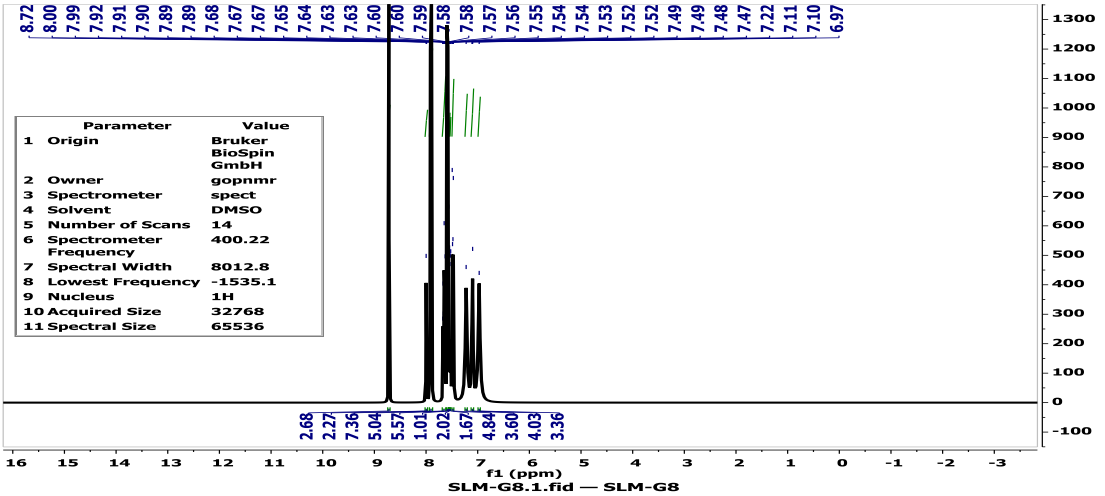


Fig3:(^{1}H.N.M.R) of compound(A_8)

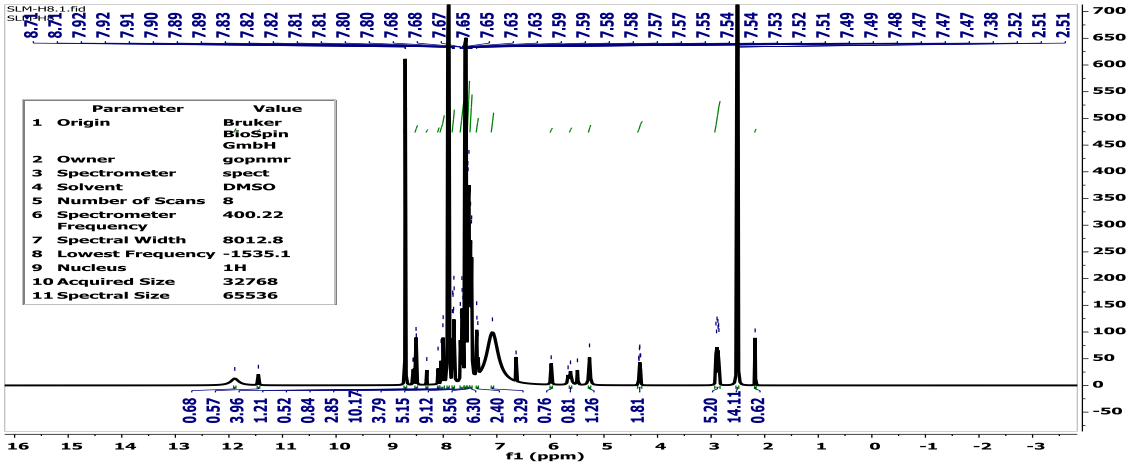


Fig4:(^{1}H.N.M.R) of compound(A_{18})

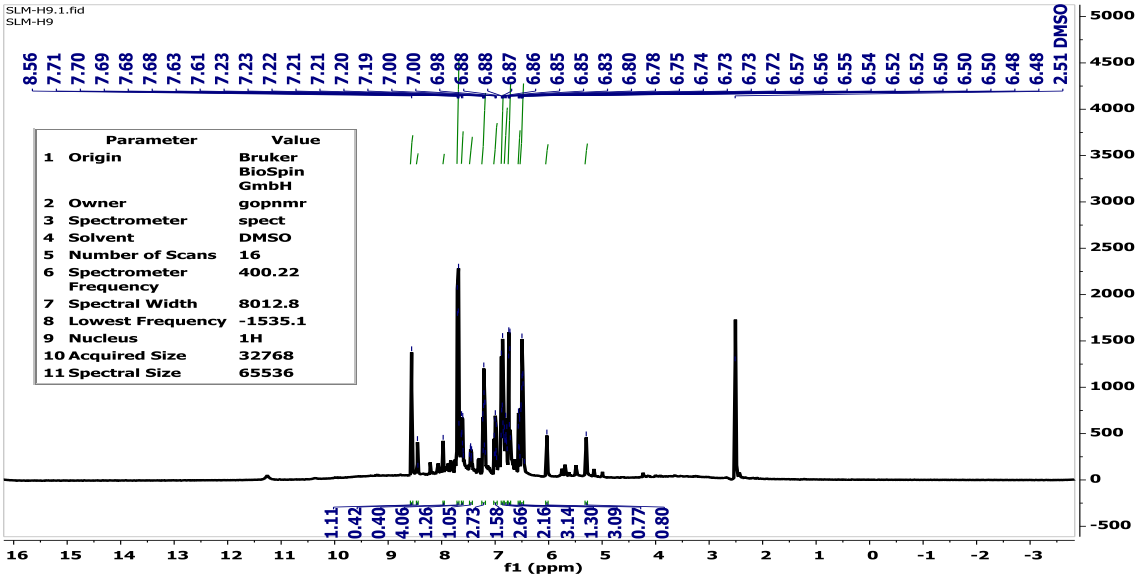


Fig5:(^{1}H.N.M.R) of compound(A_{19})

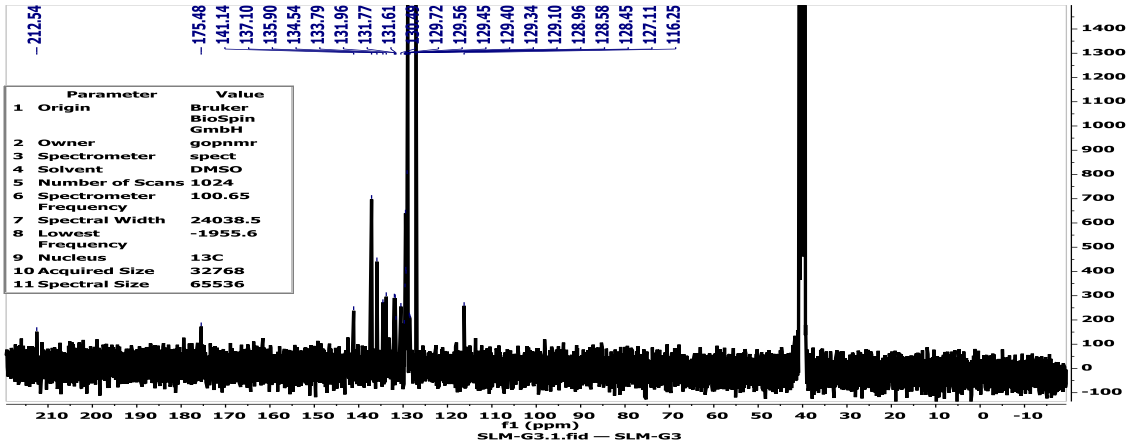


Fig6:(^{13}C.N.M.R) of compound(A_3)

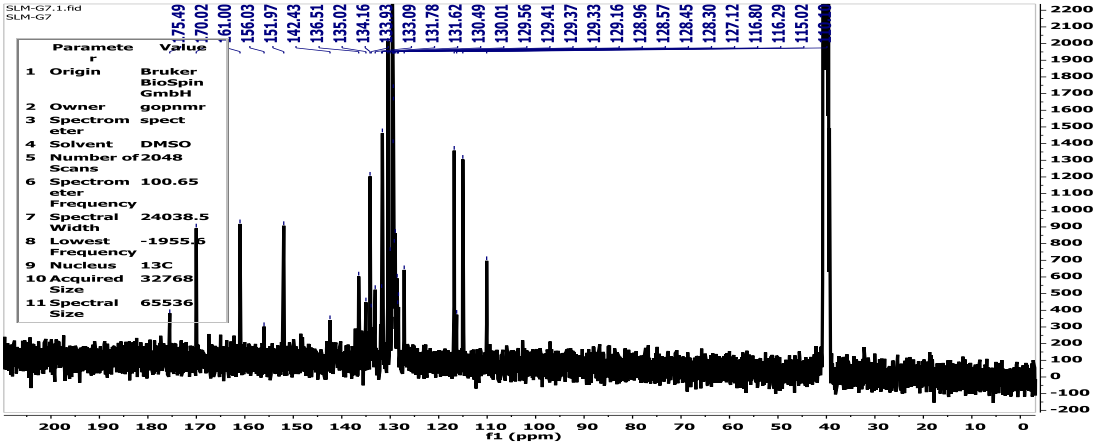


Fig 7:(^{13}C.N.M.R) of compound(A_7)

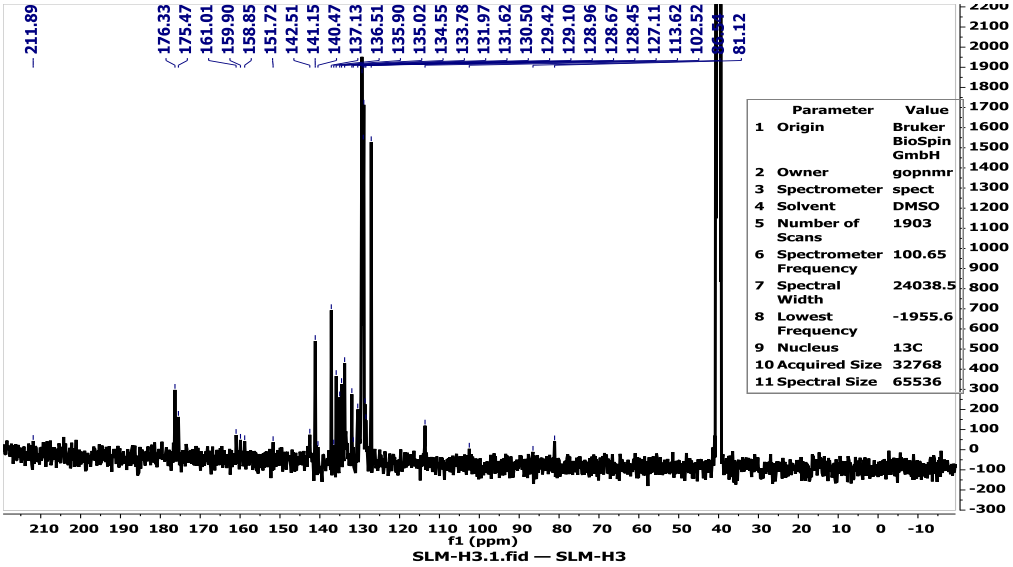


Fig 8:(^{13}C.N.M.R) of compound(A_{13})

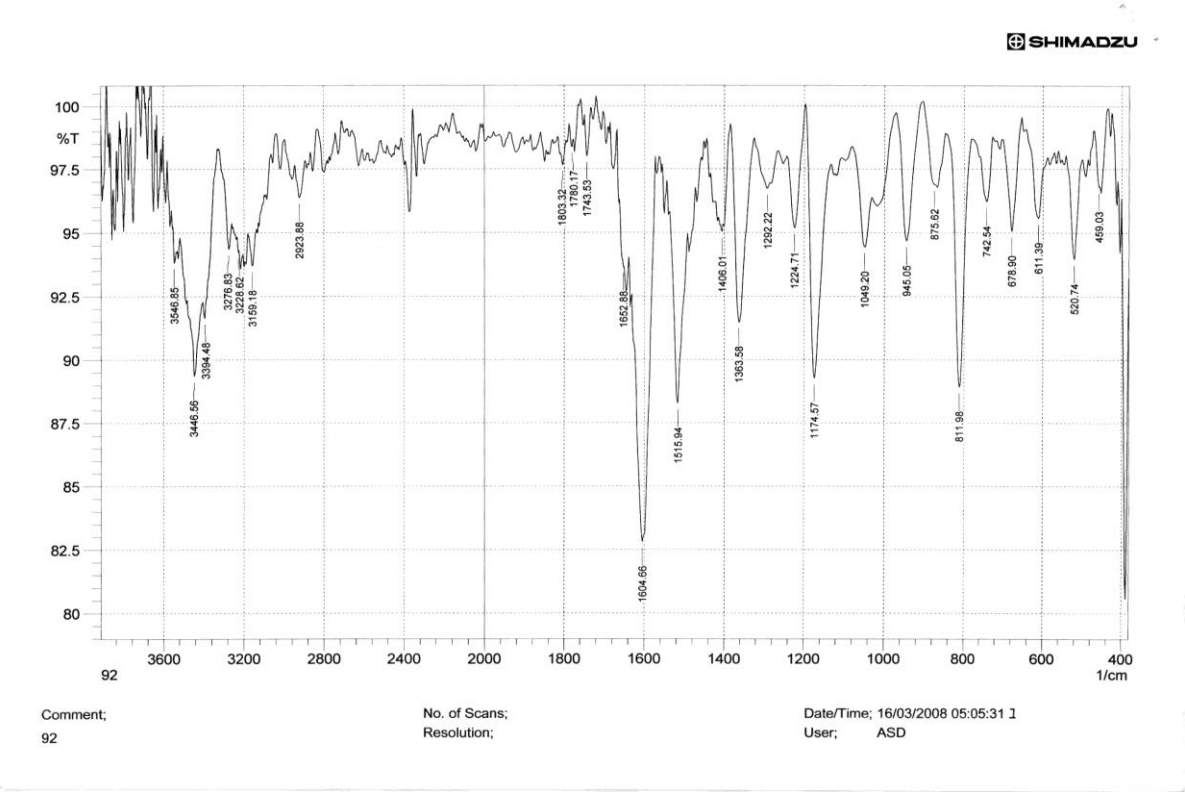


Fig 9:(IR) of compound(A_2)

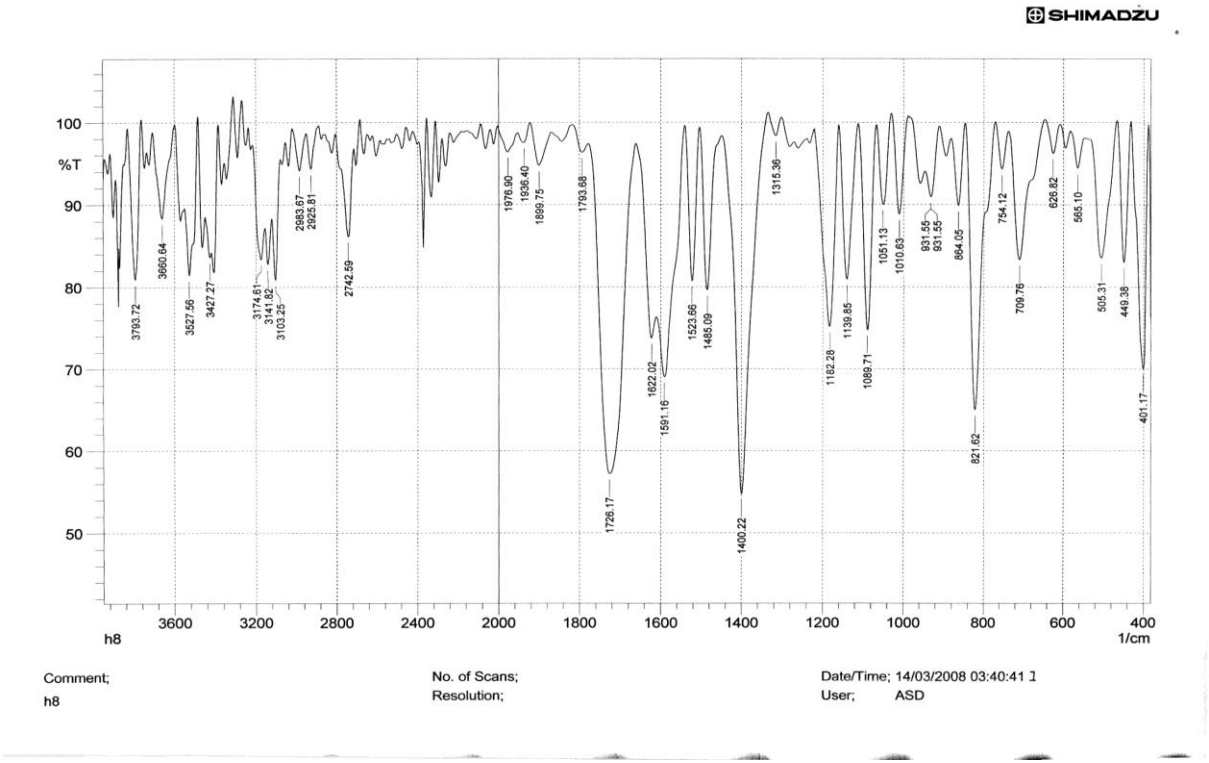


Fig 10:(IR) of compound(A_3)

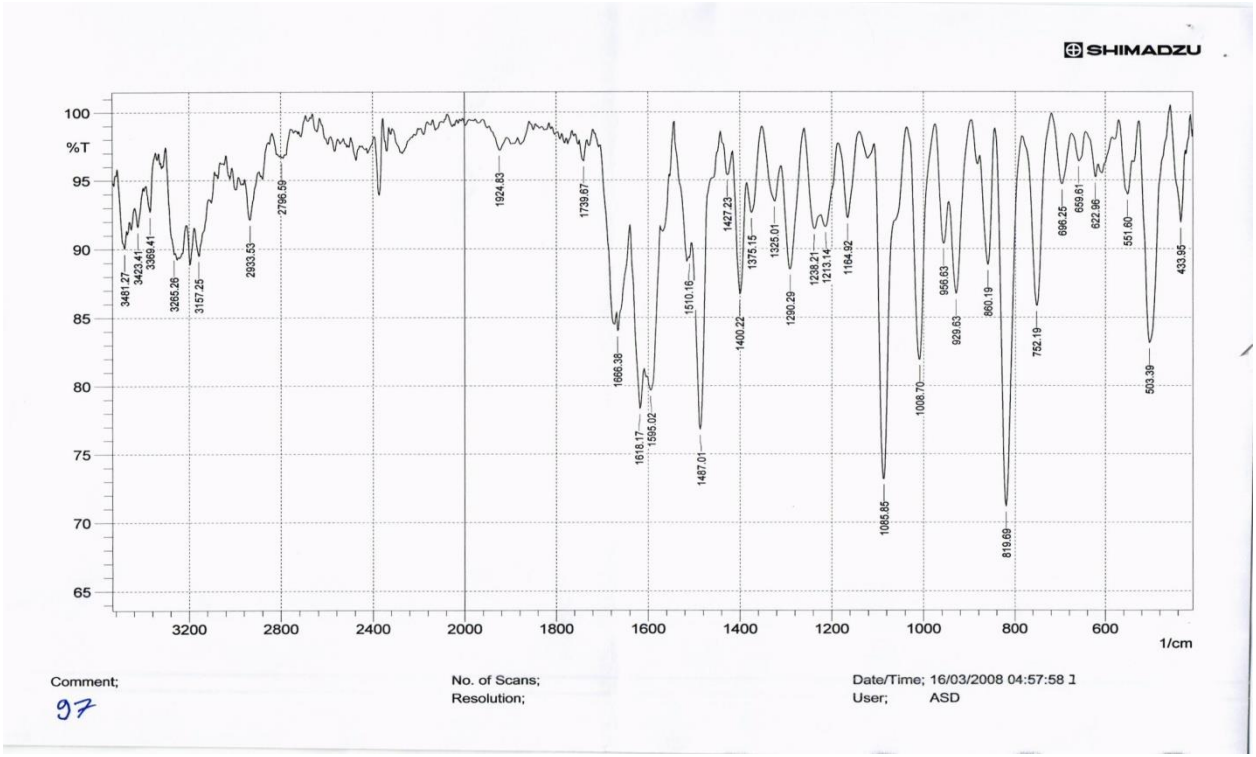


Fig 11:(IR) of compound(A_7)

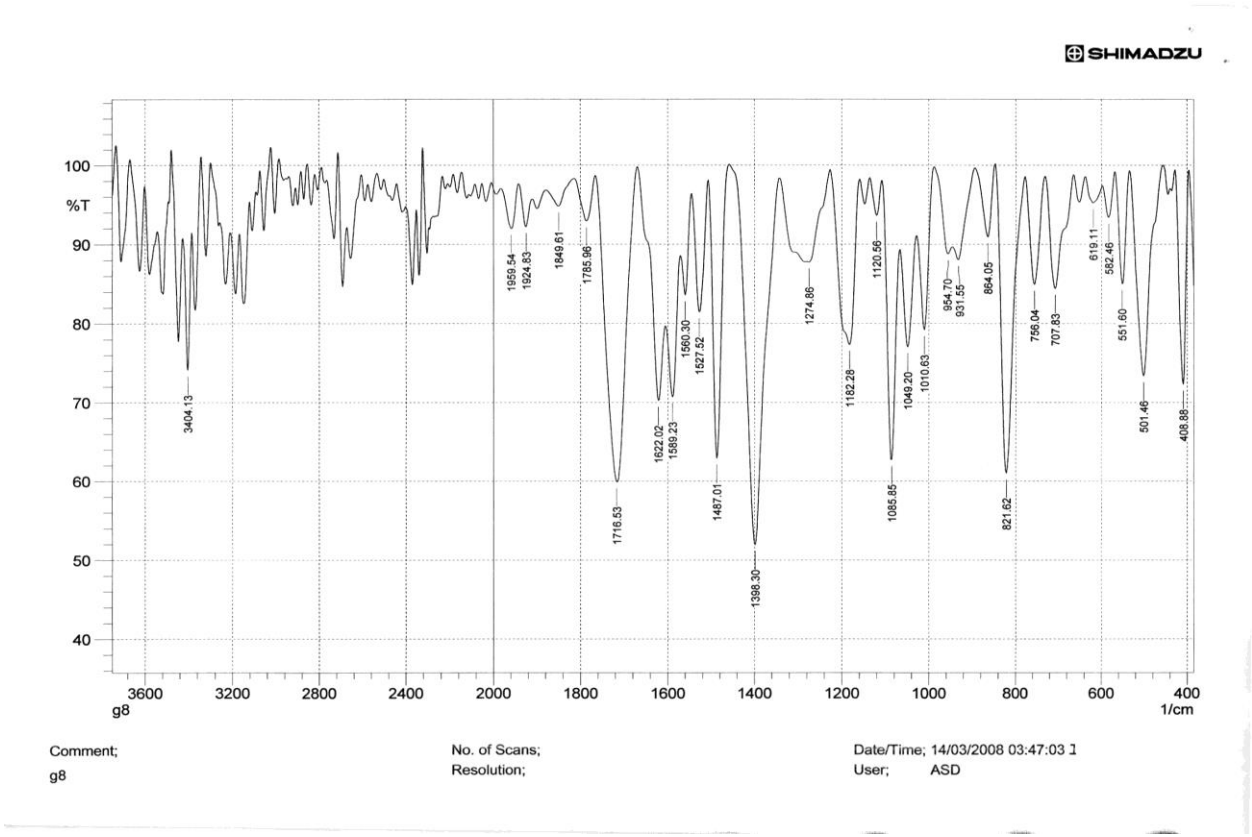


Fig 12:(IR) of compound(A_8)

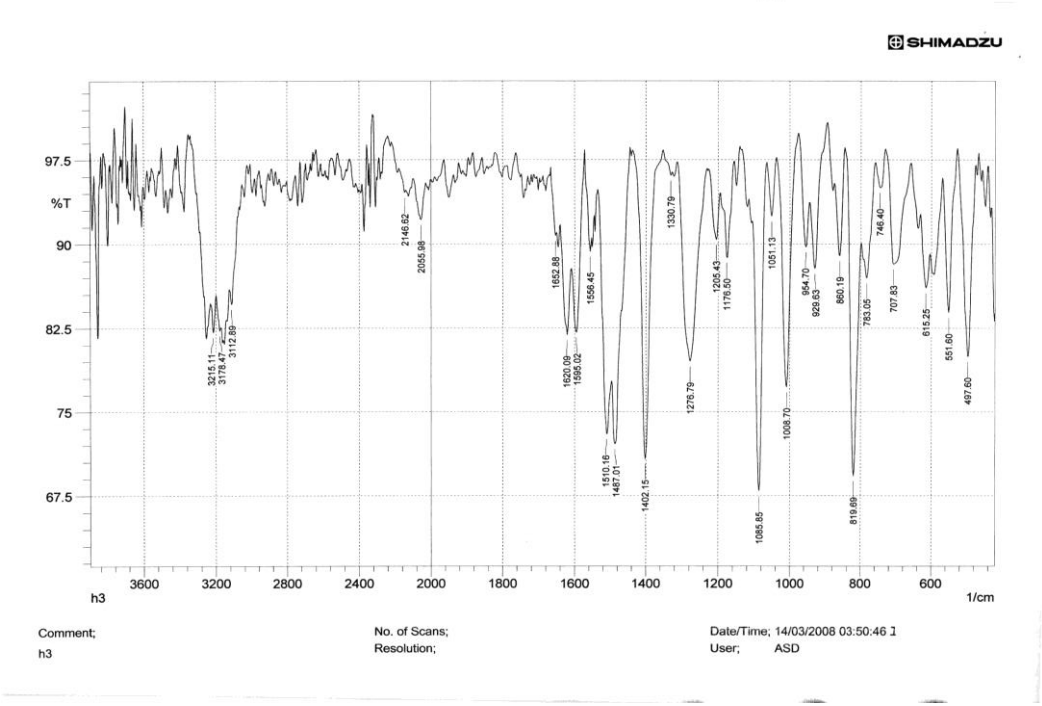


Fig13:(IR) of compound(A_{18})

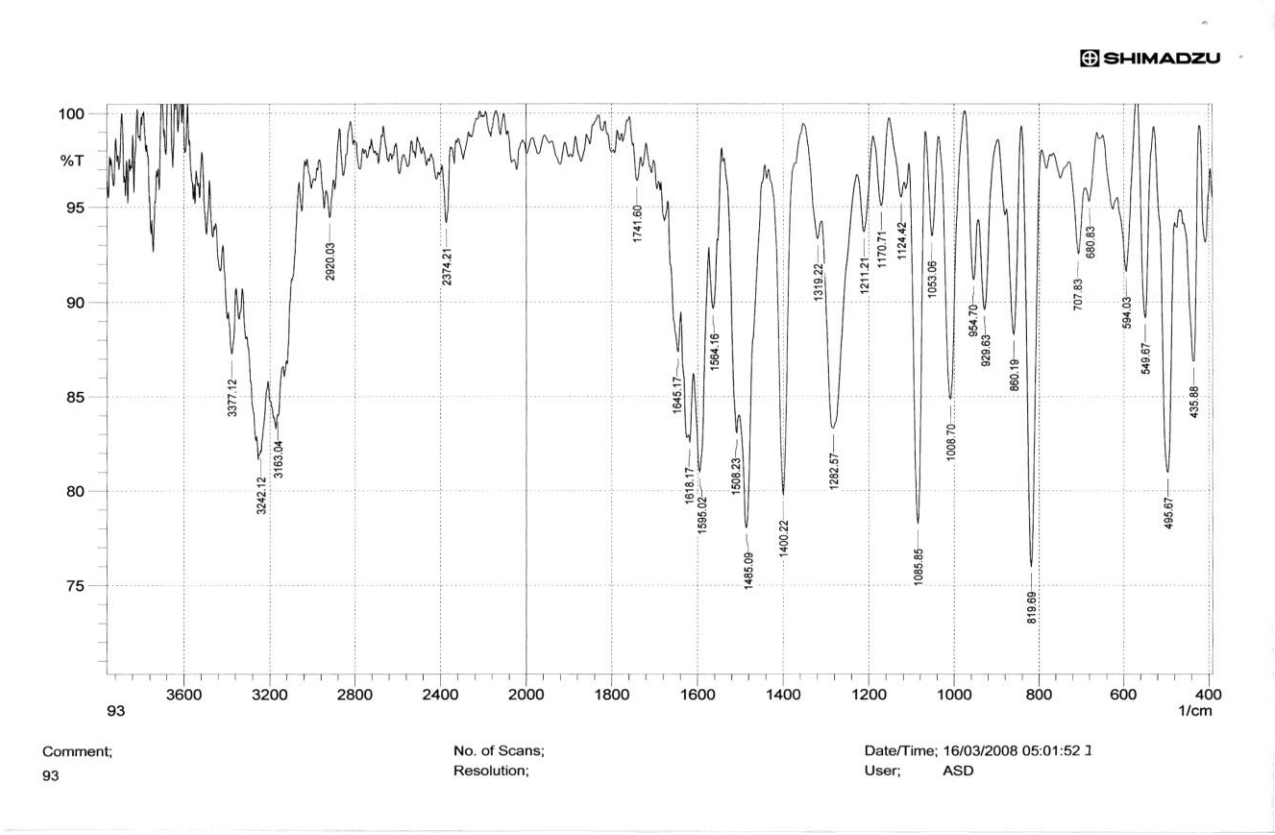


Fig14:(IR) of compound(A_{18})

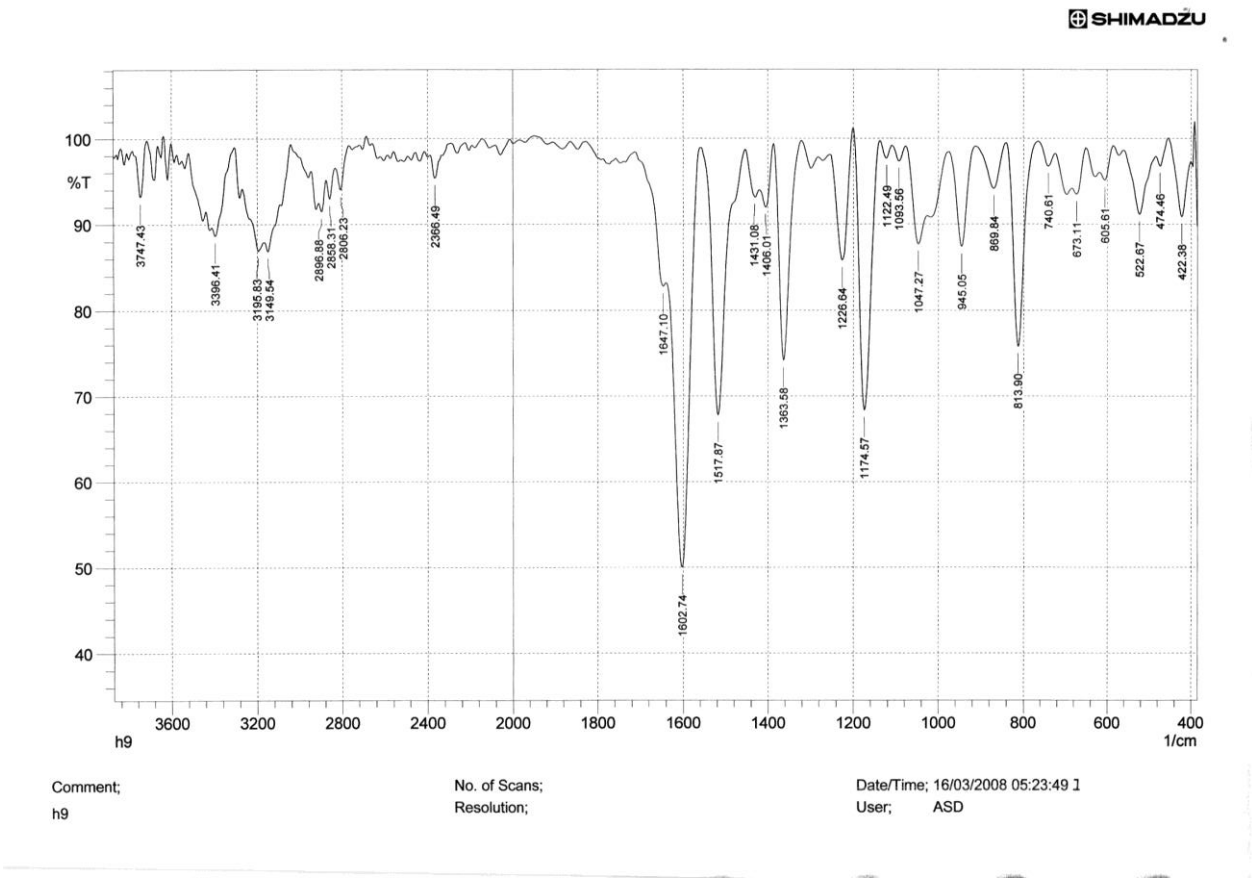


Fig 15 :(IR) of compound(A_{19})

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