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Journal of Chemical and Pharmaceutical Research, 2017, 9(1):209-219

Research Article

ISSN : 0975-7384
CODEN(USA) : JCPRC5

Synthesis, Characterization and Antimicrobial Activity of Some New Heterocyclic Compounds from Meldrum Acid

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ABSTRACT

This paper discuss a series of Meldrum acid derivatives and 4- quinolone,4-chloroquinoline derivatives which demonstrate a wide range of biological activity. In the present investigation Meldrum acid is taken as starting material and treated with different aromatic amines afforded Phenylamine(methylene Meldrum's acid)derivatives, Which further cyclazation in diphenyl ether yielded 4-quinolone derivatives. The quinolone derivatives reacted with ($POCl_3$) gives substituted 4-chloro quinoline. Some of The synthesized compounds were characterized by FT-IR, ^{1}H-NMR and C^{13}-NMR, Some the synthesis compounds were screened in vitro antimicrobial for biological activity.

Keywords: Meldrum acid; 4-quinolone; 4-chloroquinoline

INTRODUCTION

Meldrum acid (2,2-dimethyl-1,3-dioxane-4,6-dione) is an active methylene compound with rigid cyclic structure and high acidity (pka = 4.9) and undergo hydrolysis very easily [1,2] It is well known that Meldrum acid can undergo Knoevenagel condensation [3,4]. They are useful intermediates for the synthesis of heterocyclic compounds with potential pharmacological activities [5]. Quinoline is a heterocyclic aromatic organic compound featuring nitrogen atom as part of the ring system, with the chemical formula C_9H_7N [6]. It can also be named as, benzopyridine, benzo[b]pyridine, 1- benzazine and benzazine. It is a colorless hygroscopic liquid with a strong odor [7-11]. Quinoline is a weak tertiary amine which is obtained by *o*-condensation of benzene ring with pyridine [12]. Quinoline is one of the most popular N-hetero aromatic compounds included into the structures of many pharmaceuticals. Predominantly the quinoline skeleton used for the design of many synthetic compounds with diverse pharmacological properties [13-20].

MATERIALS AND METHODS

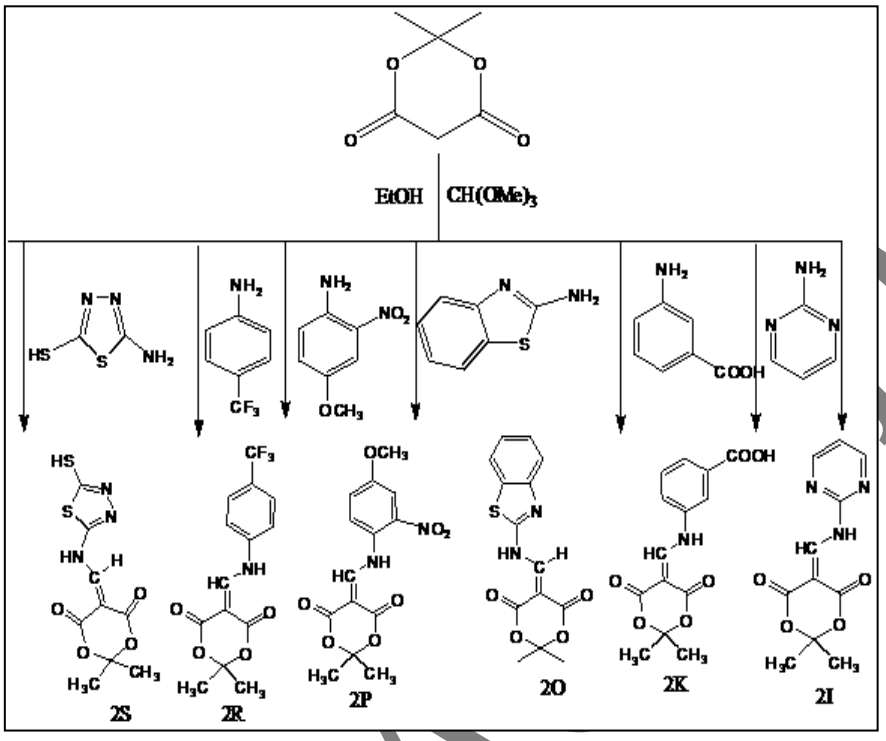
All chemicals were of highest purity and used as supplied by Fluka and Sigma-company. Measurements melting points, electro thermal 9300, melting point engineering LTD, U.K of the synthesized compounds were determined in open capillary tube, All measurements were carried out by: FT-IR spectra,Fourier transform infrared shimadzu (8400),H^1-NMR&C^{13}-NMR-spectra in (ppm) –unit were obtained in DMSO solution using (Bruker, Ultra Shield 300 MHz Switzerland), (Iran). Thin layer chromatography (T.L.C) was performed on silica gel for (T.L.C) and spots were visualized by Iodine vapors.

Synthesis of compounds (2K,2I,2O,2P,2R,2S) [21]

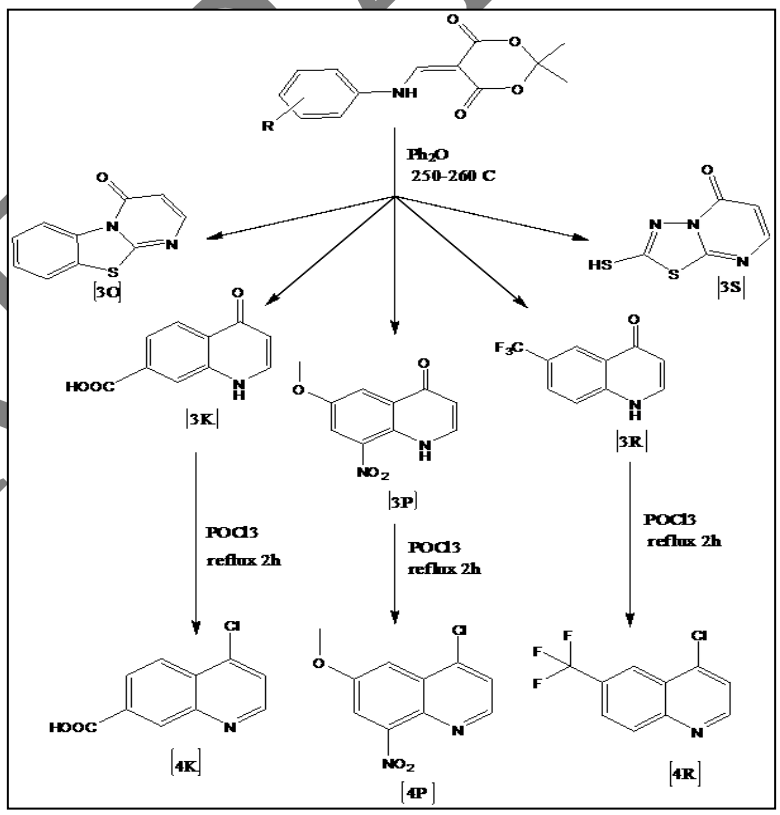
Mixture of Meldrum's acid (0.85 g, 6 mmol) and HC (OMe) 3 (1.5 mL, 12.5 mmol) was heated under reflux for 4 h,and the reaction mixture was then evaporated to dryness. The residuewas dissolved in EtOH (10mL), aromatic amine (5 mmol) was added, and the reaction mixture was stirred at ambient temperature overnight. The resulting precipitate was filtered off, washed with EtOH, and recrystallized from EtOH.

Synthesis of compounds (3K,3O,3P,3R,3S and 4F,4P,4R) [22]

(1 m mol) of (2K,2O,2P,2R,2S) was added to Ph_2O (15ml). The reaction mixture was heated at 260 ◦C for 30 min, and then quickly cooled to room temperature, and the precipitate was filtered off and washed with n-hexane and add to phosphoryl chloride (4 ml) the resulting mixture was reflux for (2 h) poured onto ice and water (40 ml), neutralized with 10% NaOH extracted with CH_2Cl_2 (3× 20 mL) and the combined organic layers dried ($MgSO_4$).



Scheme (1) Synthesis of compounds [2K,2I.2O,2P,2R,2S]



Scheme (2) Synthesis of Compounds (3K,3O,3P,3R,3S,4K,4P,4R)

RESULTS AND DISCUSSION

The formation of compounds[2K,2I,2O,2P,2R,2S] proceed via reaction between Meldrum acid and different aromatic amines followed by cyclization reaction to produce quinolone derivatives [3K,3O,3P,3R,3S].Then some quinolone derivatives react with oxyphosphoryl chloride to produce 4-chloroquinoline derivatives.
The structures of these compounds were confirmed by [FT-IR, H-NMR, 13C-NMR-analysis]

Table 1: FT-IR –data (cm^{-1}) of compounds

Comp No	FT-IR (KBr, cm^{-1})
2K	1726(υC=O)$_{Acid}$, 1668-1631(υC=O)$_{Ketone}$, 1595 (υC=C)$_{Alkene}$, 1500-1490 (υC=C)$_{Aromatic,}$ 1244 (υC-O), 2950(υC-H)$_{Aliphatic,}$ 3155(υN-H), 3400(υO-H) $_{Benzoic\ acid,}$ 1271(υC-N).,
2I	1743-1691(υC=O)$_{Ketone}$, 1614(υC=N) $_{Pyrimidin,}$1564 (υC=C)$_{Alkene}$, 1209 (υC-O), 2995(υC-H)$_{Aliphatic,}$ 3431(υN-H), 1269(υC-N).
2O	1735-1700 (υC=O)$_{Ketone}$, 1661(υC=N) 1604(υC=C)$_{Alkene}$, 1581-1529 (υC=C) $_{Aromatic,}$ 1224 (υC-O), 2904(υC-H)$_{Aliphatic,}$ 3240(υN-H), 1282(υC-N), 659(υC-S).
2P	1728-1689 (υC=O)$_{Ketone}$, 1598 (υC=C)$_{Alkene}$, 1529(υC=C)$_{Aromatic,}$ 1219 (υC-O), 2943(υC-H)$_{Aliphatic,}$ 3213(υN-H), 1273(υC-N), 1350(υ NO_2).
2R	1735-1689 (υC=O)$_{Ketone}$, 1639 (υC=C)$_{Alkene}$, 1612-1591 (υC=C)$_{Aromatic,}$ 1274 (υC-O), 2945(υC-H)$_{Aliphatic,}$ 3224(υN-H), 1313(υC-N), 810(υ C-F).
2S	1724-1683 (υC=O)$_{Ketone}$, 1608(υC=N) 1539(υC=C)$_{Alkene}$, 1230 (υC-O), 2939(υC-H)$_{Aliphatic,}$ 3228(υN-H), 1286(υC-N), 717(υ C-S),2680(υ S-H)
3K	1695(υC=O)$_{Acid}$, 1658(υC=O)$_{Ketone}$, 1591 (υC=C)$_{Alkene}$, 1548 (υC=C)$_{Aromatic,}$ 3151(υN-H), 3363(υO-H) $_{Benzoic\ acid,}$ 1282(υC-N).
3O	1666 (υC=O)$_{Ketone}$, 1585(υC=N) 1529(υC=C)$_{Alkene}$, 1581-1487(υC=C)$_{Aromatic,}$ 1238 (υC-O), 1284(υC-N), 690(υ C-S).
3P	1668 (υC=O)$_{Ketone,}$1637 (υC=C)$_{Alkene}$, 1606(υC=C)$_{Aromatic,}$ 1192 (υC-O), 2974(υC-H)$_{Aliphatic,}$ 3263(υN-H), 1236(υC-N), 1321-1535(υ NO_2).
3R	1662(υC=O)$_{Ketone}$, 1643 (υC=C)$_{Alkene}$, 1602 (υC=C)$_{Aromatic,}$ 1255 (υC-O),, 3226(υN-H), 1332(υC-N), 835(υ C-F)
3S	1666 (υC=O)$_{Ketone}$, 1637-1614 (υC=N) 1548(υC=C)$_{Alkene}$, 1236 (υC-O), 1300(υC-N), 752(υ C-S),2600(υ S-H), 3121(C-H) $_{Alkene.}$
4K	1672(υC=O)$_{Acid}$, 1633 (υC=N), 1593 (υC=C)$_{Aromatic,}$ 3350(υO-H) $_{Benzoic\ acid,}$ 837(υC-Cl).
4P	1652 (υC=N), 1606(υC=C)$_{Aromatic,}$ 1064 (υC-O), 2939(υC-H)$_{Aliphatic,}$ 1236(υC-N), 1346-1529(υ NO_2), 864 (υC- Cl).
4R	1641 (υC=N), 1589 (υC=C)$_{Aromatic,}$ 758(υ C-F), 866(υC- Cl).

Their FT-IR-Spectrum, showed an absorption band at (1743-1662) cm^{-1} due to carbonyl group, other bands appeared at (1639-1564) cm-1, (3431-3169) cm^{-1} due (C=C) alkene group & (N-H) group, respectively. in compounds (4K,4P,4R) absorption band at (1690-1625) cm^{-1} due to (C=N) group. and other bands are summarized in table (1).

Table 2: H-NMR (δ ppm, DMSO) of Compounds

Comp. No.	H-NMR
2K	δ 1.69 (s,6H,CH_3), δ 7.67-7.99 (m,4H,Arom.), δ8.66(s,1H,CH=C), δ 11.30-11.34 (1H,NH), δ 13.00(1H,COOH)
2I	δ 1.69 (s,6H,CH_3), δ 7.39-8.80 (m,3H$_{Pyrimidine}$), δ 9.07-9.11 (s,1H,CH=C), δ11.02-11.05(1H,NH).
2O	δ 1.6 (s,6H,CH_3), δ 7.39-7.83(m,4H), δ 8.79-8.83(s,1H,CH=C),δ 11.07 (1H,NH)
2P	δ 1.70 (s,6H,CH_3), δ 3.89(s,3H,OCH_3) δ 7.45-8.03(m,4H), δ 8.67(s,1H,CH=C), δ 12.49-12.53(1H,NH)
2R	δ 1.69 (s,6H,CH_3), δ 7.75-7.82(m,4H), δ 8.66(s,1H,CH=C), δ 11.33 (1H,NH)
2S	δ 1.68 (s,6H,CH_3), δ 8.53 (s,1H,CH=C), δ 12.00(1H,NH), δ 14.27 (s, IH, SH)
3K	δ 7.09-7.18 (q,2H, CH =CH_3), δ 7.52-8.05(m,4H)
3O	, δ 11.31-11.34 (1H,NH), δ 12.98(1H,COOH)
3P	δ 6.17-7.16 (d,2H, CH_2=CH_3), δ 3.89(s,3H,OCH_3) δ 7.37-8.15(m,2H), δ 11.76(1H,NH)
3R	δ 6.15-7.78 (d,2H, CH_2=CH_3), δ 7.91-8.35(m,4H), δ 12.11 (1H,NH)
3S	δ 6.93-7.41 (m,2H, CH_2=CH_3), δ4.55 (s,1H,SH).
4K	δ 7.42 H_3, δ 8.37 H_2, δ 7.71 -7.94 – 8.54(H_8- H_6-H_5), δ11.76 (1H,$COOH_)$
4P	7.40 H_3, δ 8.20 H_2, δ 7.60 -7.82 – 8.01(H_8- H_6-H_5)

Table 3: C13-NMR-data (δ ppm, DMSO) of Compounds

Comp. No.	C^{13}-NMR
2K	104.81-131.29 (C_1-C_6)$_{Phenyl\ ring}$, 88.31 C_{12}, 153.49 C_8,142.63 C_9, 163.09-164.21 C_{10}, C_{14}, 167.04 $C_{(COOH)}$, 26.99 $C_{15,16}$.
2I	105.11-151.19 (C_1-C_4)$_{Pyrimidine\ ring}$, 89.87 C_{12}, 159.41 C_8,151.22 C_9, 163.50 -164.76 C_{10}, C_{14}, 26.60 $C_{15,16}$
2P	104.99-153.79 (C_1-C_6)$_{Phenyl\ ring}$, 89.31 C_{12}, 157.16 C_8,139.32 C_9, 162.86-164.48 C_{10}, C_{14}, 27.00 $C_{15,16}$. 56.70 $C_{(OCH3)}$
2R	104.78-127.15 (C_1-C_6)$_{Phenyl\ ring}$, 88.44 C_{12}, 153.80 C_8,142.47 C_9, 163.07-164.13 C_{10}, C_{14}, 26.97 $C_{15,16}$.
2S	(105.21 C_2, 186.63 C_4)$_{Thiadiazole\ ring,}$ 91.47 C_{12}, 154.25 C_8,150.24 C_9, 162.53-162.85 C_{10}, C_{14}, 27.15 $C_{15,16}$.
3K	168.33 (C_4), 167.09 (C)$_{(COOH)}$, 114.89(C_3), 132.77 (C_2), 117.09-139.58 (C) $_{Phenyl\ ring.}$
3P	175.51 (C_4), 109.57(C_3), 137.57 (C_2), 115.25-140.72 (C) $_{Phenyl\ ring,}$ 56.45-56.87 (C)$_{(OCH3)}$.
3R	176.80 (C_4), 110.33(C_3), 140.96 (C_2), 119.05-142.63 (C) $_{Phenyl\ ring.}$
3S	181.35 (C_4), 109.72(C_3), 155.48 (C_2), 161.95 (C)$_{(C\text{-}SH),}$ 176.52 (C)$_{Thiadiazole}$
4K	121.32C_3, 155.09 C_2, 139.79 C_4, 129.89 $C_{4'}$, 125.08 C_5, 128.19 C_6, 130.75 C_8,132.34 C_7, 130.90 $C_{8'}$, 166.91 $C_{(COOH).}$

Their H^1-NMR-Spectra, showed peaks at (1.68-1.70), (8.47-9.07),(11.02-12.49) due to protons of (CH_3) methyl group, (CH=C=) alkene group, (N-H) group), respectively in compounds [2K-2S] peaks at (6.15-6.39) due to (CH=CH) in compounds [3R,3S], other signals of functional groups show in table (2).

Their C^{13}-NMR-Spectra, The measurement indicate to formation of compounds in this work, as shown in table (3).

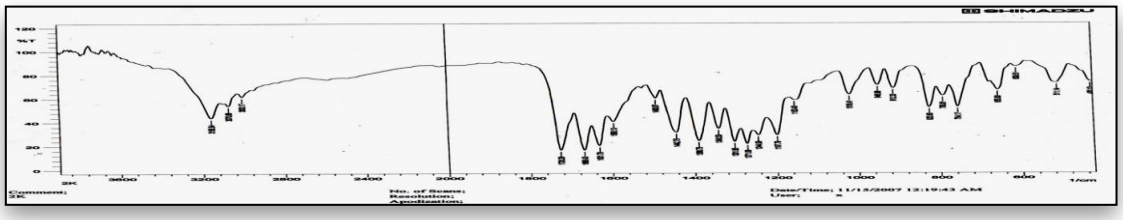


Figure 1: FT-IR Spectrum of Comp. (2K)

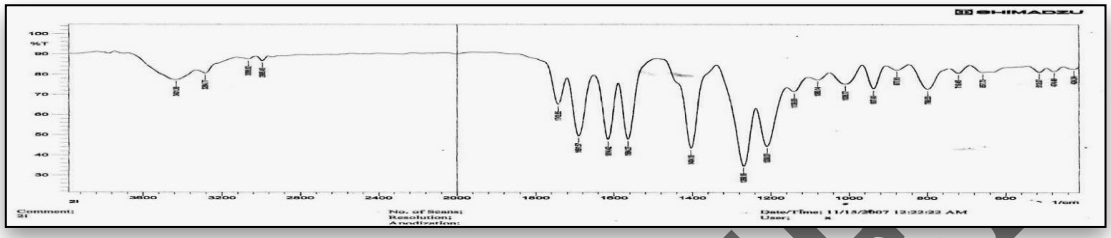


Figure 2: FT-IR Spectrum of Comp. (2I)

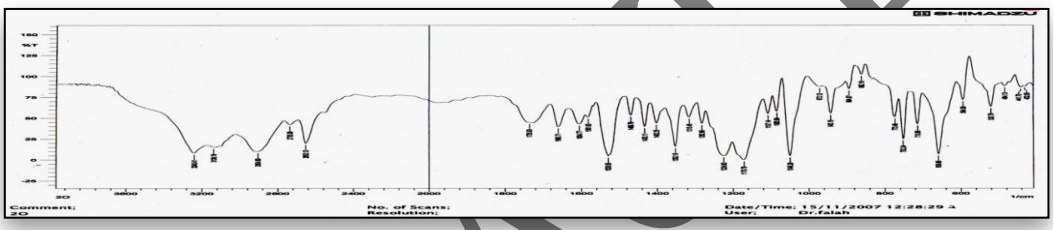


Figure 3: FT-IR Spectrum of Comp. (2O)

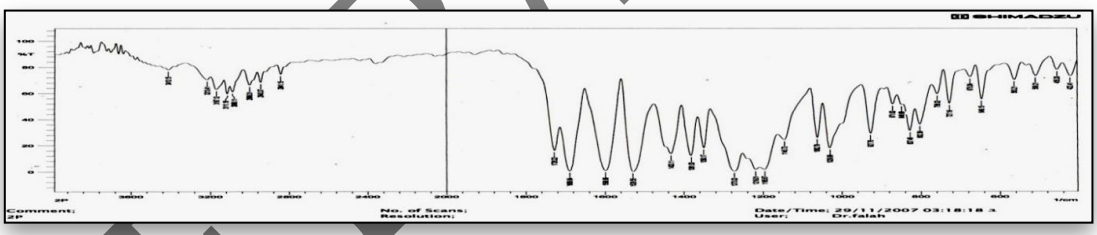


Figure 4: FT-IR Spectrum of Comp. (2P)

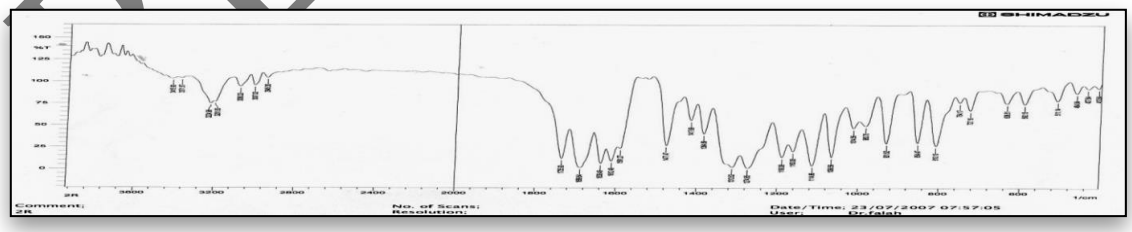


Figure 5: FT-IR Spectrum of Comp. (2R)

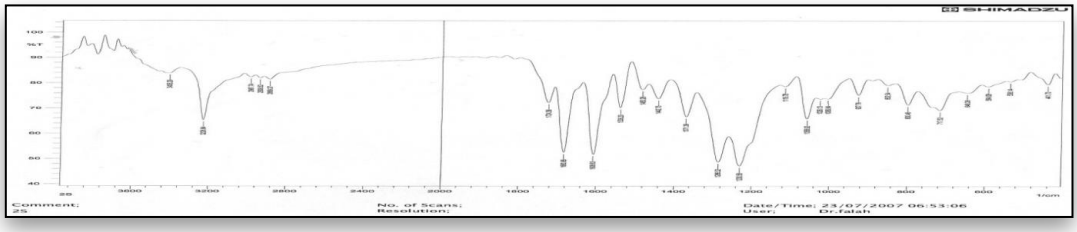


Figure 6: FT-IR Spectrum of Comp. (2S)

Table 4: Physical properties of synthesis compounds

Comp. No.	Color	m.p (+2) °C	Yield %	M.Wt	M.F
2K	Orange	161	82	291	$C_{14}H_{13}NO_6$
2I	white	170	85	249	$C_{11}H_{11}N_3O_4$
2O	pink	153	69	304	$C_{14}H_{12}N_2O_4S$
2P	yellow	204	86	322	$C_{14}H_{14}N_2O_7$
2R	yellow	195	83	315	$C_{14}H_{12}F_3NO_4$
2S	Pale yellow	155	81	287	$C_9H_9N_3O_4S_2$
3K	Pale yellow	247	73	189	$C_{10}H_7NO_3$
3O	Pale pink	187	66	202	$C_{10}H_6N_2OS$
3P	Drak yellow	183	71	221	$C_{10}H_8N_2O_4$
3R	brown	176	52	213	$C_{10}H_6F_3NO$
3S	yellow	201	64	185	$C_5H_3N_4OS_2$
4K	yellow	211	67.7	207	$C_{10}H_6ClNO_2$
4P	Black	251	67	238	$C_{10}H_7ClN_2O_3$
4R	Pale brown	263	50	231	$C10H_5ClF3N$

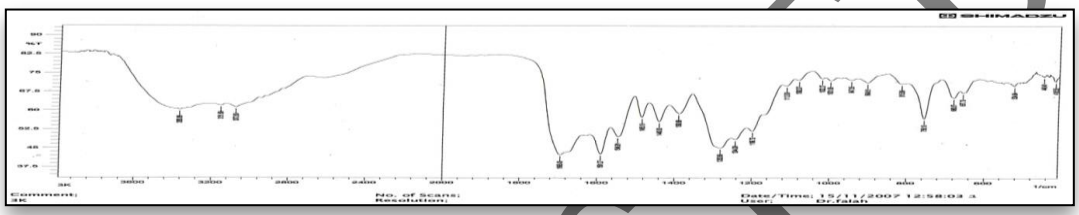


Figure 7: FT-IR Spectrum of Comp. (3K)

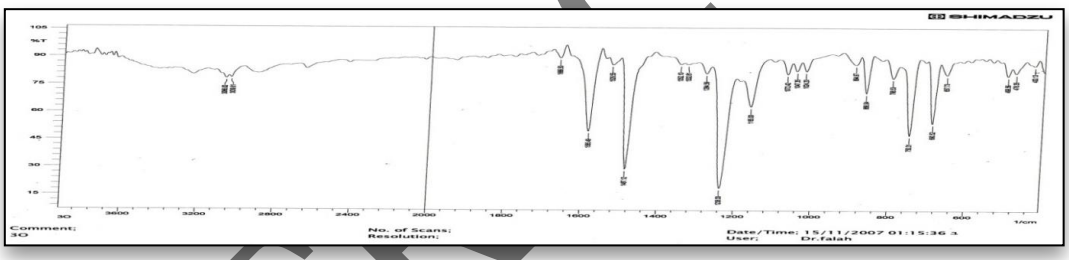


Figure 8: FT-IR Spectrum of Comp. (3O)

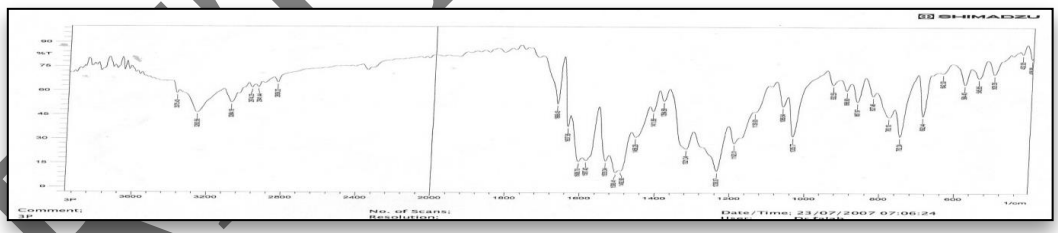


Figure 9: FT-IR Spectrum of Comp. (3P)

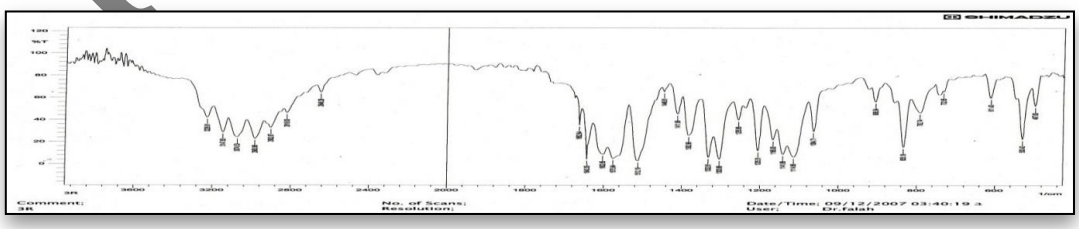


Figure 10: FT-IR Spectrum of Comp. (3R)

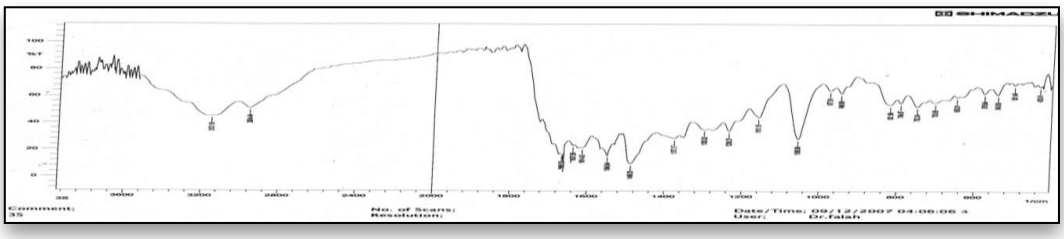


Figure 11: FT-IR Spectrum of Comp. (3S)

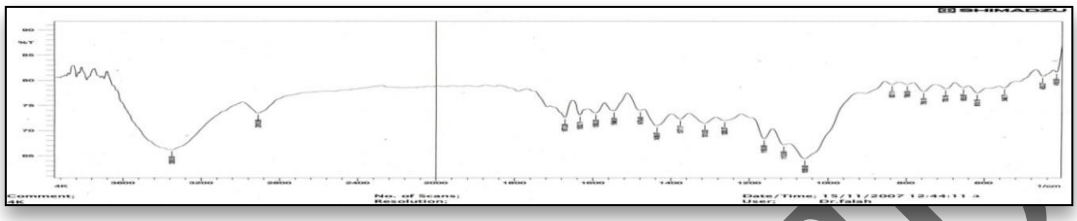


Figure 12: FT-IR Spectrum of Comp. (4F)

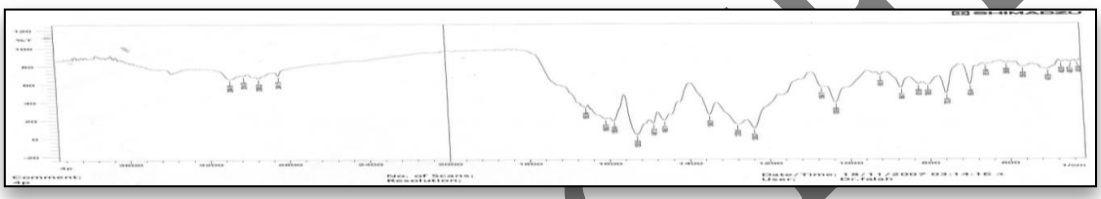


Figure 13: FT-IR Spectrum of Comp. (4P)

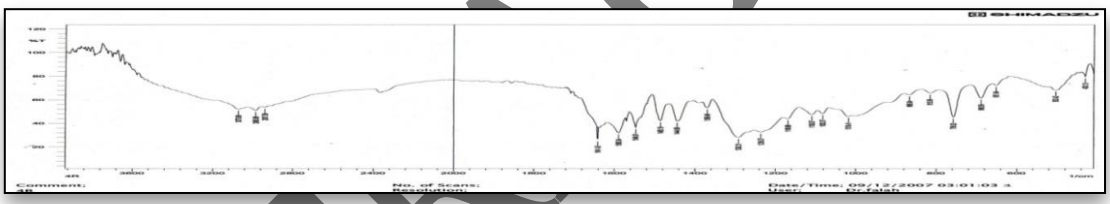


Figure 14: FT-IR Spectrum of Comp. (4R)

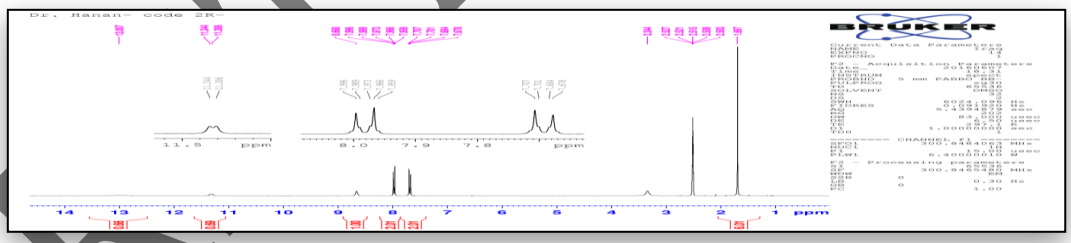


Figure 15: H1-NMR Spectrum of Comp. (2K)

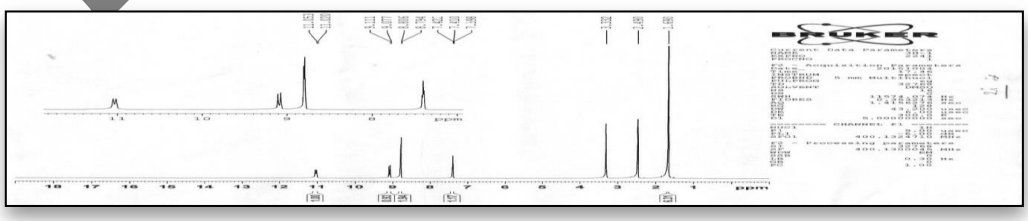


Figure 16: H1-NMR Spectrum of Comp. (2I)

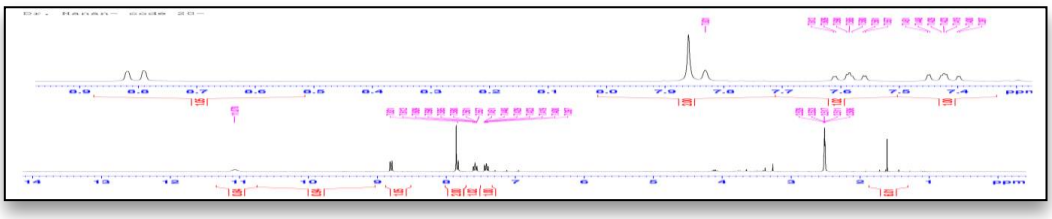


Figure 17: H1-NMR Spectrum of Comp. (2O)

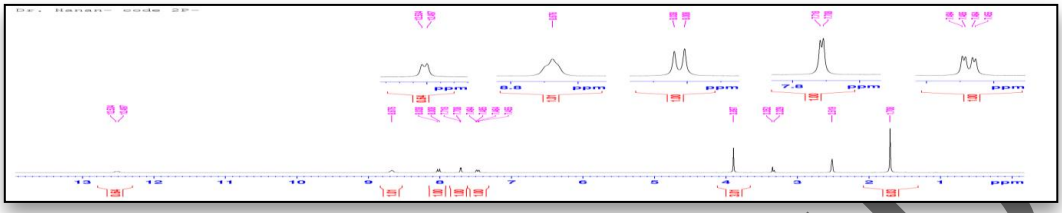


Figure 18: H1-NMR Spectrum of Comp. (2P)

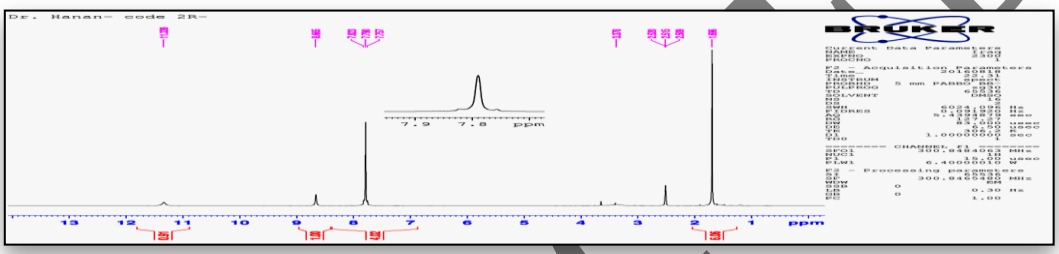


Figure 19: H1-NMR Spectrum of Comp. (2R)

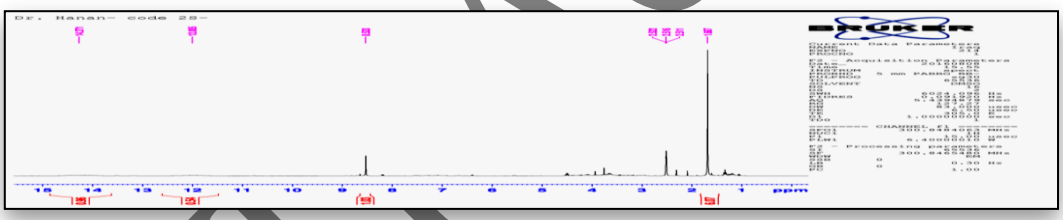


Figure 20: H1-NMR Spectrum of Comp. (2S)

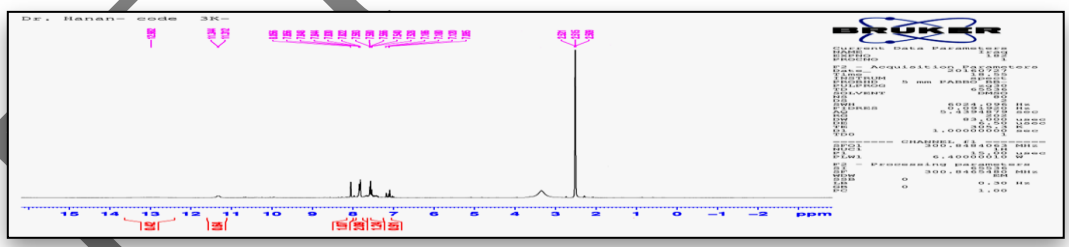


Figure 21: H1-NMR Spectrum of Comp. (3K)

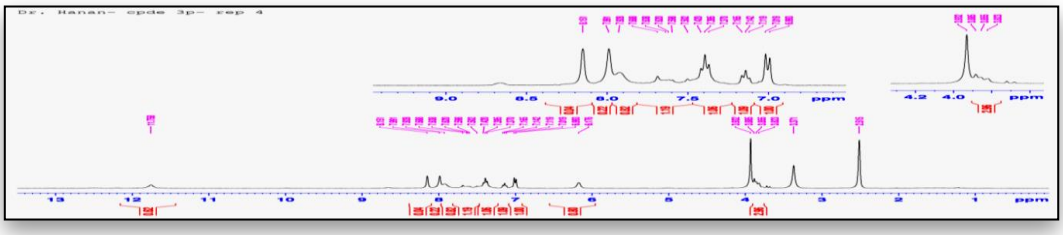


Figure 22: H1-NMR Spectrum of Comp. (3P)

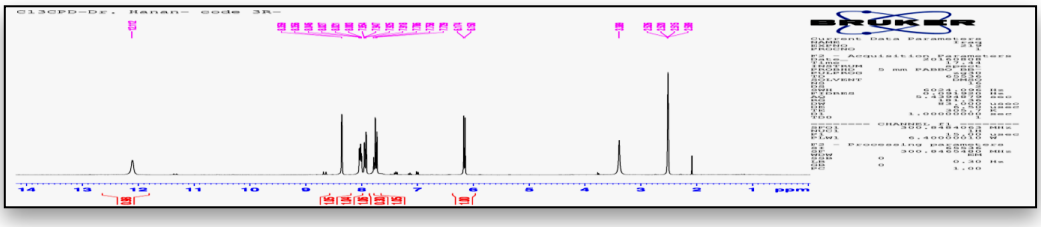


Figure 23: H1-NMR Spectrum of Comp. (3R)

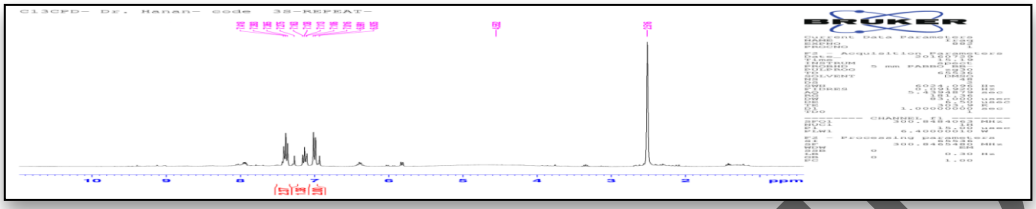


Figure 24: H1-NMR Spectrum of Comp. (3S)

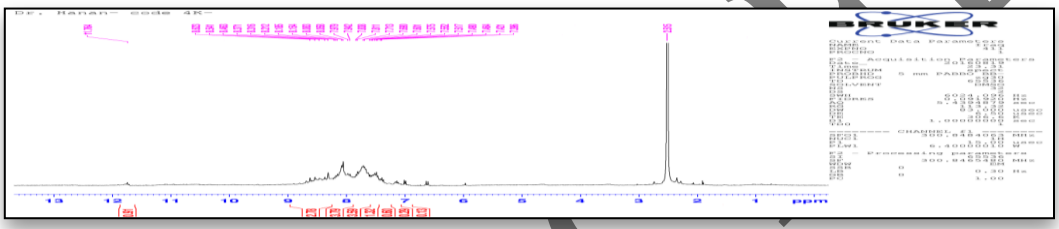


Figure 25: H1-NMR Spectrum of Comp. (4K)

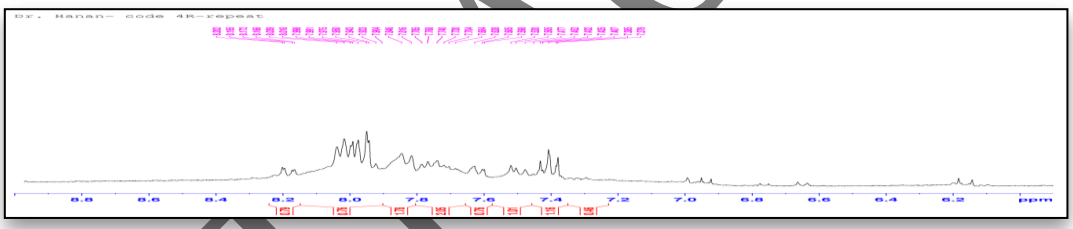


Figure 26: H1-NMR Spectrum of Comp. (4R)

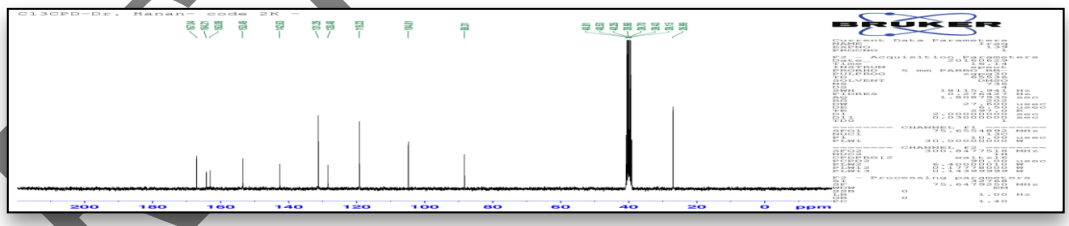


Figure 27: C13-NMR Spectrum of Comp. (2K)

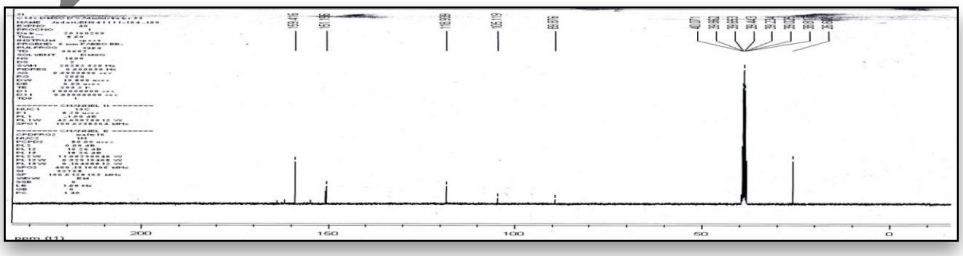


Figure 28: C13-NMR Spectrum of Comp. (2I)

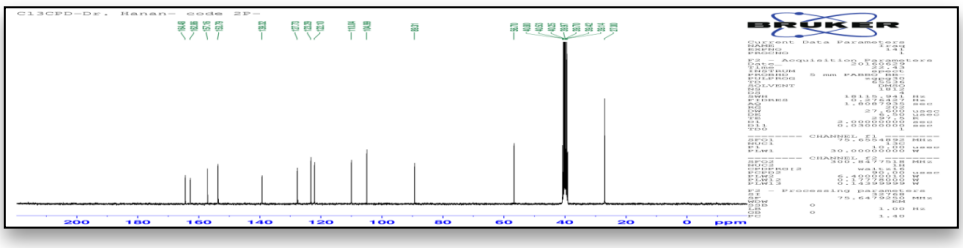


Figure 29: C13-NMR Spectrum of Comp. (2P)

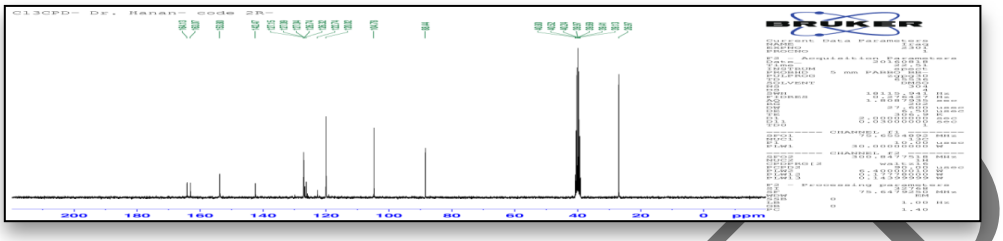


Figure 30: C13-NMR Spectrum of Comp. (2R)

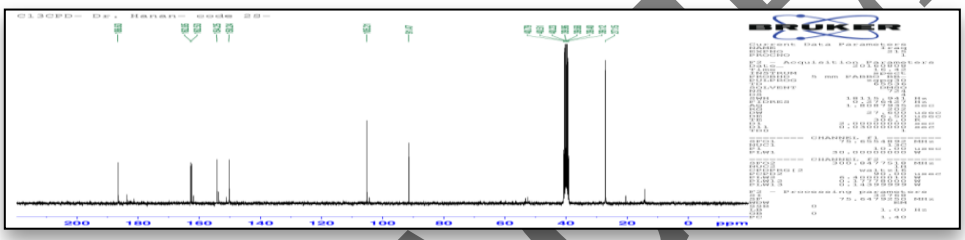


Figure 31: C13-NMR Spectrum of Comp. (2S)

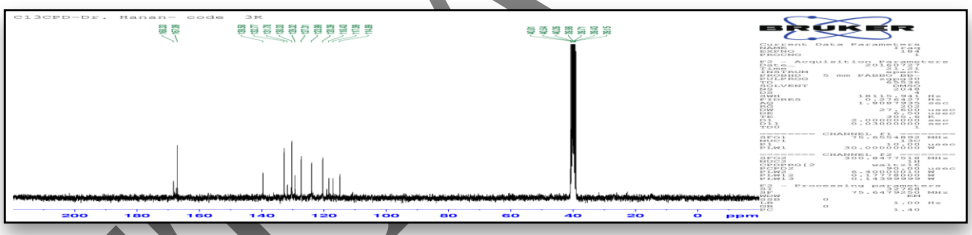


Figure 32: C13-NMR Spectrum of Comp. (3K)

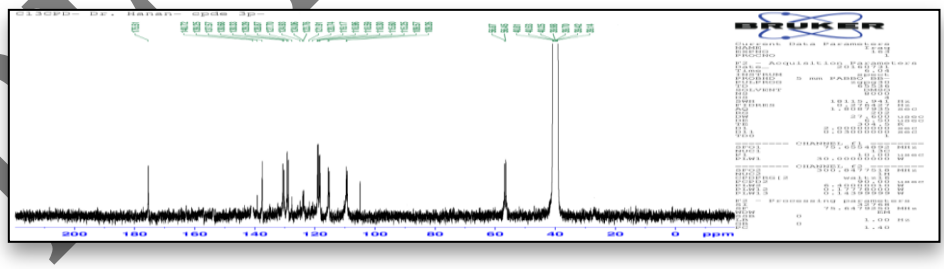


Figure 33: C13-NMR Spectrum of Comp. (3P)

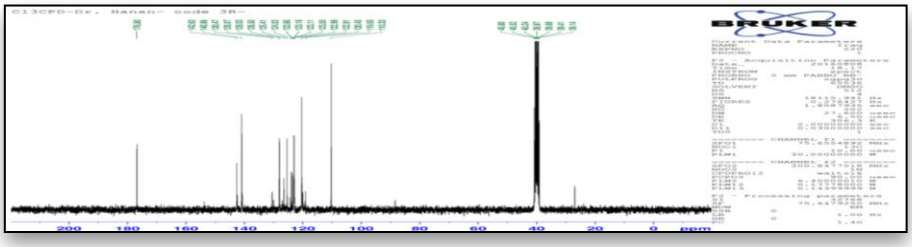


Figure 34: C13-NMR Spectrum of Comp. (3R)

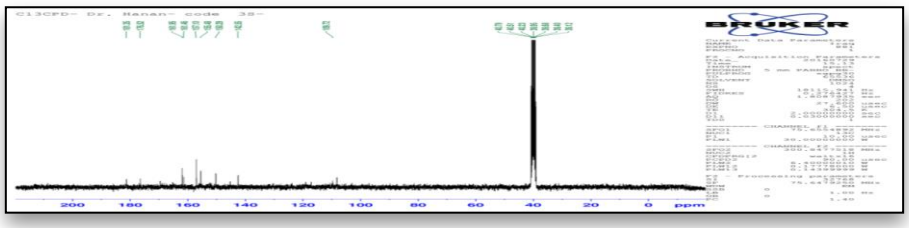


Figure 35: C13-NMR Spectrum of Comp. (3S)

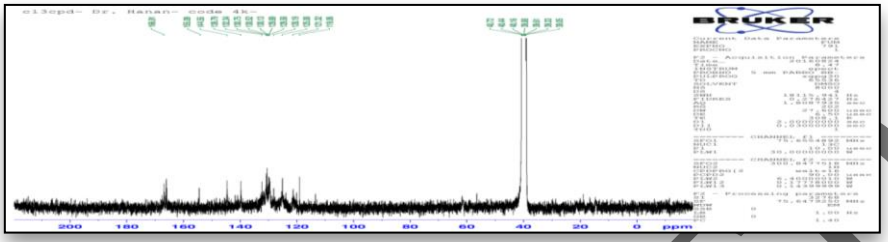


Figure 36: C13-NMR Spectrum of Comp. (4K)

Assay of Antimicrobial Activity [23]

An antibacterial activity has been conducted according to Piercing method, Some of prepare compounds were tested by the method against four types of bacteria *gram negative* such as *Escherichia coli*, and *gram positive* like *Staphylococcus aureus*, *Streptococcus pneumonia*. All compounds were dissolved in 3 dissimilar concentration 5mg, 10mg, 15mg in 5ml DMSO, the surface of solid culture media (Nutrient Agar) dried and applied on the plates which had been streaked with standardized bacterial inoculums and incubated at 37 ^{o}C for 24h. This technique is based on the determination of an inhibited zone (in mm) proportional to the bacteria in the plates.

Table 5: Antibacterial activity for some of synthetic compounds

Comp. No.	Inhibition zone (mm) 5 10 15 (mg/ml)		
	Escherichia coli	*Staphylococcus aureus*	*Streptococcus pneumonia*
2O	8 10 13	8 9 11	- - -
2P	10 12 15	12 15 24	6 8 11
2R	10 15 19	11 15 18	- - -
3p	15 18 20	18 22 26	- - -
3S	10 14 17	9 11 14	- - -
3R	9 13 18	10 13 17	- - -
4K	8 11 14	9 12 15	
4P	11 14 16	15 20 24	

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