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Condensation of some N-phthalylaminoacid with Selected Sulfa Drugs by using DCC as Condensing Agent.

Bushra K Al-Salami*, Heba H Sabah and Hanaa K Moussa.

College of Science, University of Basrah

ABSTRACT

Sulfa drug derivatives of some amino acids were synthesis from the condensation of protective amino acid, namely, N-phathalylDL–Valine, N–Phthalyl, D–Valine and N–Phthalyl-DL–Isoleucine with some Sulfa drugs like Sulfa-acetamide Sodium and Sulfanilamide by coupling them in one step by using N-N-Dicyclohexylcarbodiimide (DCC) as condensing reagent to Furnish the corresponding amide. The condensation products have been characterized by IR, elemental analysis and ^{1}H-NMR .The spectroscopic data indicate that the condensation gives products with 1:1 ratio of N-phthalylaminoacid ; Sulfa drugs. The antibacterial activity of the prepared compounds were determined against several clinical microbial isolates which are: *staphylococcus aurous and E. Coil*by using different concentrations of each compound

Keywords :N-pathalylaminoacid, DCC, Sulfa-drugs

Corresponding author

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INTRODUCTION

Amino acid are especially important nature science . They form the basis of peptides and enzymes[1,2]. Also sulfa drugs such as sulfa-acetamide sodium are synthetic antimicrobial agents with a wide spectrum encompassing most gram-positive and many gram-negative, for example sulfanilamide have been used a good drugs for disease like malaria and convulsion[3]. It was previously noted that, since the amide is thermodynamically more stable that carboxylic acid or ester linkage , the synthesis of amide fromcarboxylic acid is thermodynamically favorable[4]. It have shown that the reaction between a carboxylic acid and amine can be accelerated by usingdicyclohexylcarbodiimide(DCC)[4-6]. This reagent acts as a dehydrating agent, it removes (– OH) from the carboxylic group and H- from the amino group to form an amide bond.More specifically, DCC activates the α-carboxyl group of amino acids derivatives towardsnuclephilic acyl substitution by converting its. (– OH) group into a better leaving group[7]. In this work direct condensation between the carboxylic group from N –phthalyl amino acids with amino group of sulfa drugs at room temperature and in one-step by using DCC as condensation agent to prepare thesulfa drugs derivation of some amino acids

EXPERIMENTAL

Materials and physical measurements

All chemicals and solvents are obtained from fluka and Aldrich chemical companies. and are used without purification. Melting points were recorded on Gallenkamp melting point apparatus without further correction. IR Spectra were measured on shimadzu spectrophotometer as KBr pellets in the region 4000-400 cm^{-1}.^{1}HNMR spectra were recorded on Bruker 400MHz

Preparation of N-phthalyl amino acid

N-phthalyl amino acids used in at this study were prepared by the method describedfling and Fox i.e.(8). An equi–molar ratio of phthalic anhydride and amino acid was heated in an oil-bath at appropriate temperaturefor 30 min with continues stirring[8,9] after cooling , the solid material was extracted with boiling ether. The residue was and recrystallized from cyclohexane. The following N-phthalyl amino acids are prepared.Presented in the following table.

Table 1: Some physical properties of the prepared N-naphthyl amino acids

Amino acid derivative	Degree of Fusion	Yield %	m.p. C^o (literature)
N-phthalyl-D-Valine	145 – 150 C^o	47%	112 – 114 (113 – 114)
N-phthalyl-DL-Valine	145 – 150 C^o	52%	102 – 103 (101 – 102)
N-phthalyl-DL-isoLeucine	150 – 155 C^o	66%	121 – 122 (120 – 121)

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Synthesis of sulfa drugs derivation :

1. Sodium (4,2 –(1,3–dioxoeisoindolin–2–y1)–3–methylbutanamido)phenyl sulfonyl methyl amide
2. Sodium(4,2–(1,3–dioxoisoimdoline–2–yl)–3–methylpentaamido) phenyl sulfonyl methyl amide .
3. Sodium(4,2–(1,3–dioxoisoimdoline–2–yl)–3–methylpentaamido) phenyl sulfonyl methyl amide .
4. 2 – (1,3–dioxo isoimdoline–2–yl) –3 – methyl –N –(4 – Sulfamoyl phenyl) butanamide.
5. 2 – (1,3–dioxo isoimdoline–2–yl) –3 – methyl –N –(4 – Sulfamoyl phenyl) butanamide .
6. 2 – (1,3–dioxo isoimdoline–2–yl) –3 – methyl –N –(4 – Sulfamoyl phenyl) pentanamide .

The title compounds (1 – 6) prepared from the corresponding N-phthalylamino acid and sulfa drug via the literature procedure by Curni [10] i.e. To a stirred solution of N-phthalyl amino acid (1.0 mmol) and sulfa drug (1.0 mmol) in 50ml methylene chloride.Asolution of DCC (0.206 g, 1m mol) in 5 ml methylene chloride was added dropwise to a solution of N-phthaly amino over a period of 15 min at room temperature. After the addition was complete the mixture stirred overnight . A white precipitate formed (di cyclohexylurea) was filtered5% citric acid aqueous solution was added to the flitted was separated and evaporated to drynessand the resultant organic –aqueous mixture was shaking vigorously solution. The organic layers was evaporated. The residua was dissolved in a mixture of ethylacetate and n-hexane and purified by CC.

The physical properties of the prepared compound are shown in Table 2.

Table 2: The physical properties and elemental analysis of the prepared compounds

Compound	Color and state	%Yield	m.p(^{O}C)	%C	%H	%N	%S
1	White crystal	54	174 – 176	54.91(55.26)	4.66(5.03)	9.61(10.03)	7.3(7.72)
2	White crystal	56	180 – 182	54.91(55.3)	4.66(5.03)	9.61(10.03)	7.3(7.78)
3	Pall yellow crystal	60	194 – 196	87.(56.24)	4.91(5.4)	9.31(9.69)	7.10(7.48)
4	White crystal	58	144 – 146	56.85(57.25)	4.77(5.07)	10.47(10.82)	7.99(8.39)
5	White crystal	61	169 – 171	56.85(57.20)	4.77(5.07)	10.47(10.82)	7.99(8.39)
6	White crystal	65	110 – 112	57.82(58.12)	5.09(5.54)	10.11(10.56)	7.72(8.10)

( ) Calculated .

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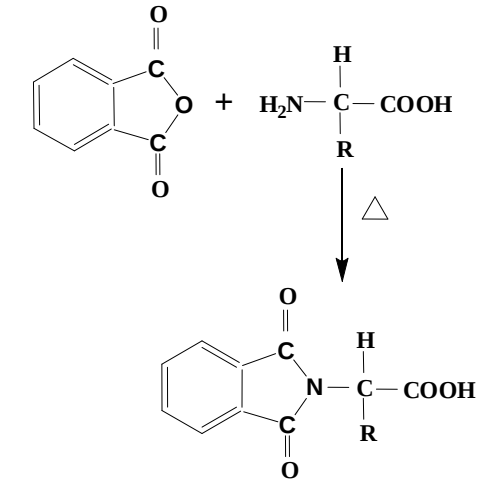
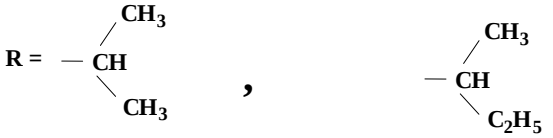
Determination of antibacterial activity

Mueller-Hinton Agar (MHA) was used to determine the sensitivity of bacteria by single disk diffusion method gainst different antimicrobial agents as described in literature [18].

RESULTS AND DISCUSSION

The reaction between amino acid and phthalic anhydride leads to formation of N-phthalylamino acid in good yield as follows in scheme1:





D-Valine
DL-Valine

DL-isoleacine

Scheme 1

The ratio reaction between sulfa drugs sodium and N-phthalylamino acid lead to formation compound (1-6) [9] in goodyield, the resulting compounds can be represented as following in scheme 2 :

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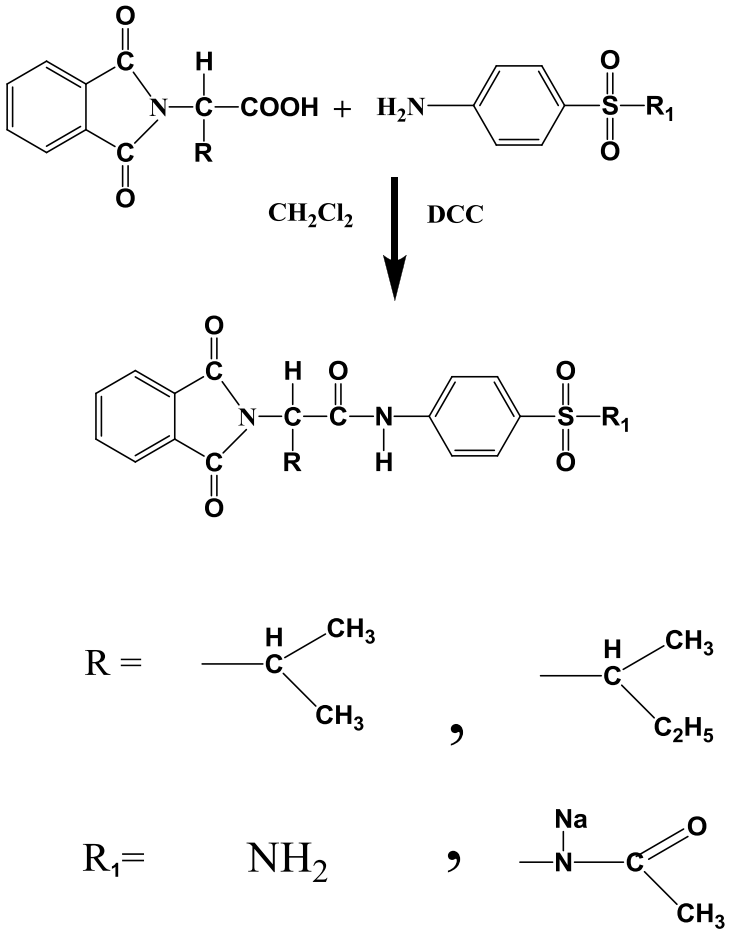

Scheme 2

The suggested mechanism for the joining of an aminefunctionfrom sulfa drug to carboxylic function group from N-protected amino acid under DCC catalysis can be summarized in scheme3 . The first step is the protonations of DCC(a). An acid base reaction followed in step in the second by addition of carboxylate anion to the C=N double bond results in electronphilic addition to C=N double bond (b). The O-acyliso-urea formed is the nitrogenanalog of a mixed anhydride (b). Nucleophilic addition of the carbonyl group of the O-acylisourea inthird step generates a tetrahedralcarbonyl addition intermediate (c) that collapses in forth step to give products (d) and dicyclohexyl urea (DCU) which separated in these reaction as a white precipitate. [7,11] Sulfa drug derivation of amino acid are shown in table (3).

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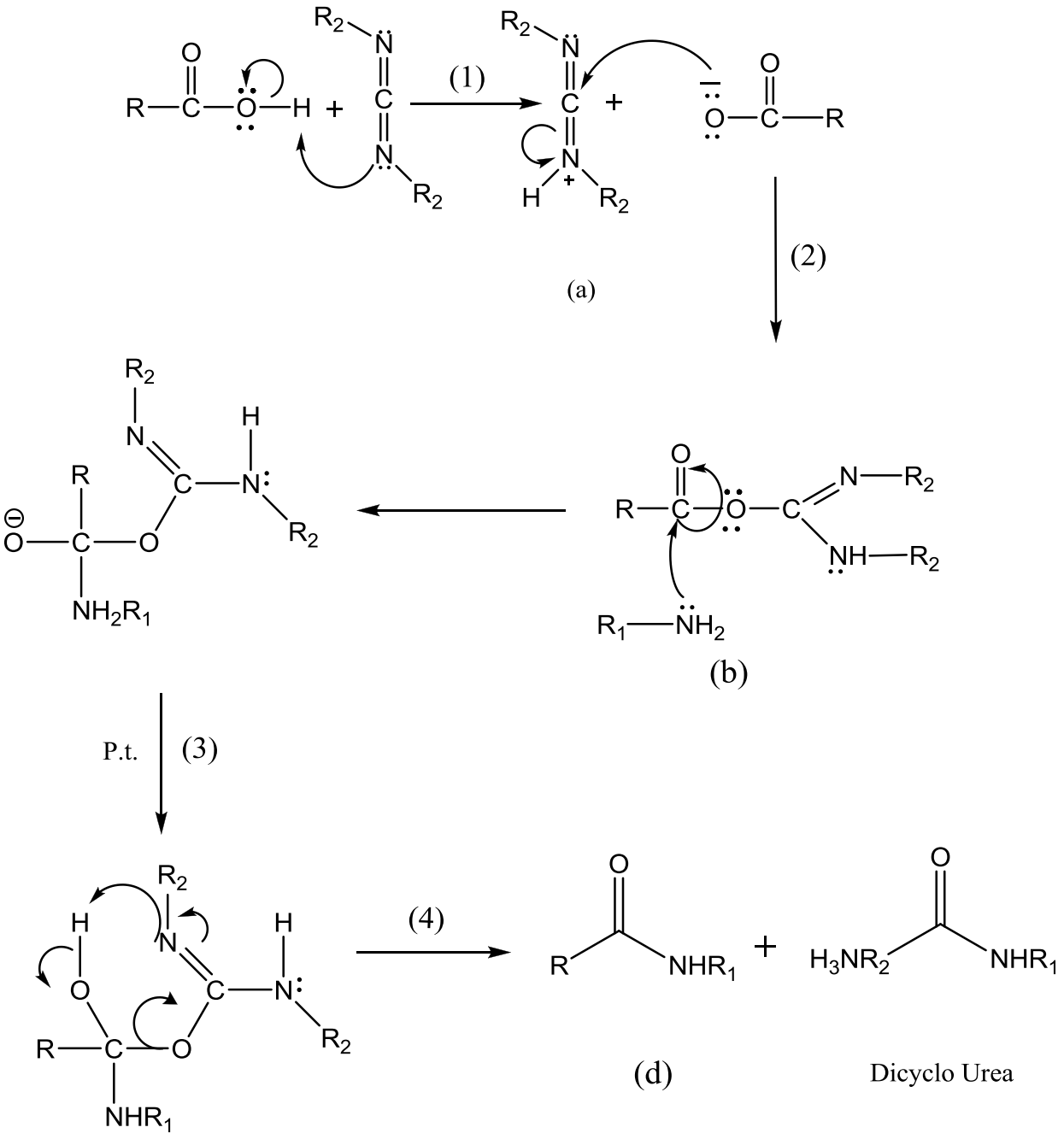

Tetrahedral carbonyl addition intermediate

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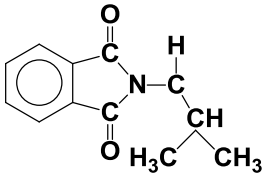
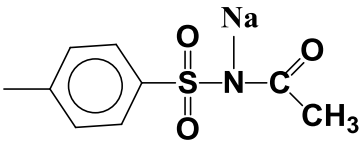
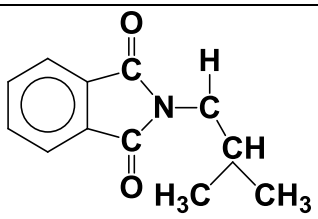
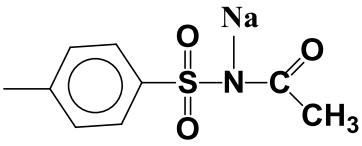
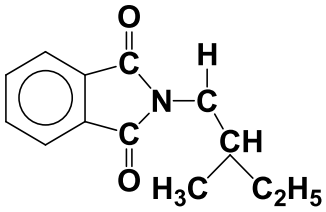
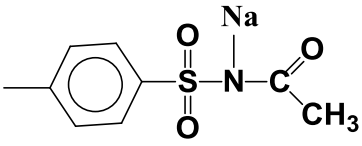
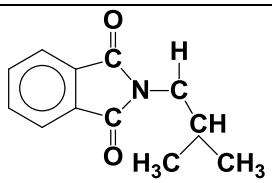
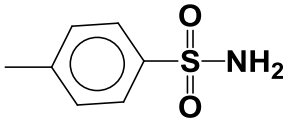
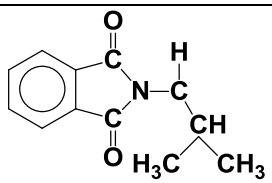
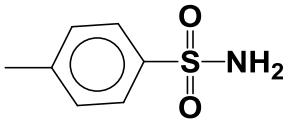
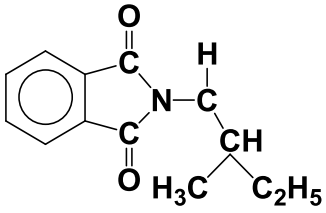
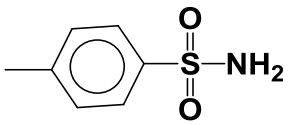
Table 3: The structures of prepared compounds.

Compound	R	R_1	R_2
1			
2			
3			
4			
5			
6			

IR Spectra

The IR spectraof Sulfa drug derivatives are shown in figure 1,2 and 3 and the IR spectral data for these compounds are summarized in Table 4 . The strong medium band at 3319 cm^{-1} is assigned to υN-H[12] stretching while the aliphatic υC-H(str) [13]. Asym and symdisplay at 2933 and 2854 cm^{-1} respectively. The amide bond formation is confirmed by the presence of the strong υN-H(amideII) band appear as very strong band at 1720 cm^{-1}also the amide I(υC=O)

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display at 1662 cm^{-1}. The very strong bands presents at 1382-1355 $cm^{-1}$and 1165-1136 cm^{-1} are assigned to asym and sym. υSO^{2}respecttively [14].

Table 4: Selected IR data for the compound cm^{-1}

Compound	υC–H Aliphatic Asy.sym	υ N–H	υC=O anhydride	υC=O amideI	υ N–H amideII	υSO_2 Asy.sym
1	2933(s) 2854(m)	3319	1830(m) 1770(m)	1720(s)	1662(m)	1382(w) 1165(w)
2	2933(S) 2852(m)	3317	1770(s) 1722(s)	1662(s)	1629(m)	1319(s) 1082(s)
3	2929(s) 2877(m)	3327	1776(m) 1712(s)	1627(s)	1627(s)	1355(m) 1087(m)
4	2931(s) 2854(s)	3332(m)	1774(m) 1724(s)	1714(s)	1629(m)	1386(s) 1074(m)
5	2929(s) 2852(m)	3327(s)	1830(w) 1772(m)	1712(s)	1662(m)	1384(s) 1085(m)
6	2918(s) 2850(m)	3327(s)	1776(m) 1712(s)	1627(s)	1612(w)	1386(s) 1087(m)

s : strong; m : medium; w : weak

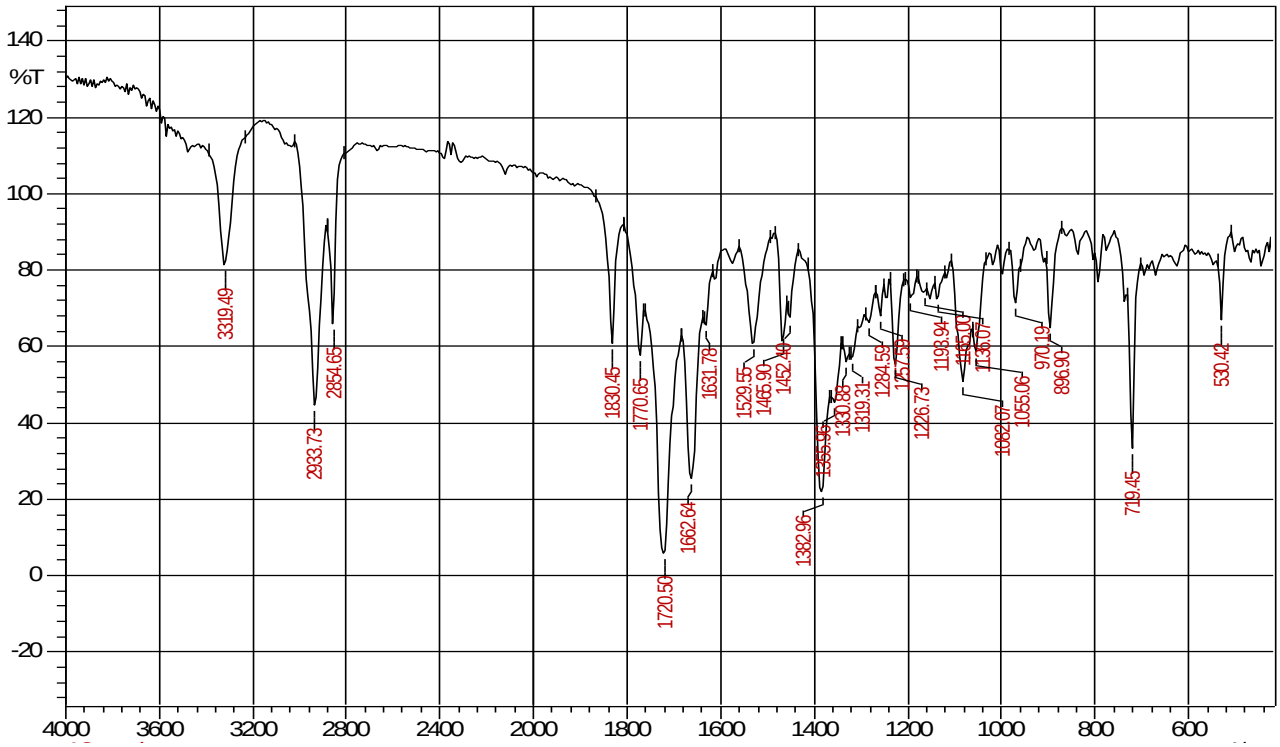

Figure 1 : The IR spectrum of Compound (1)

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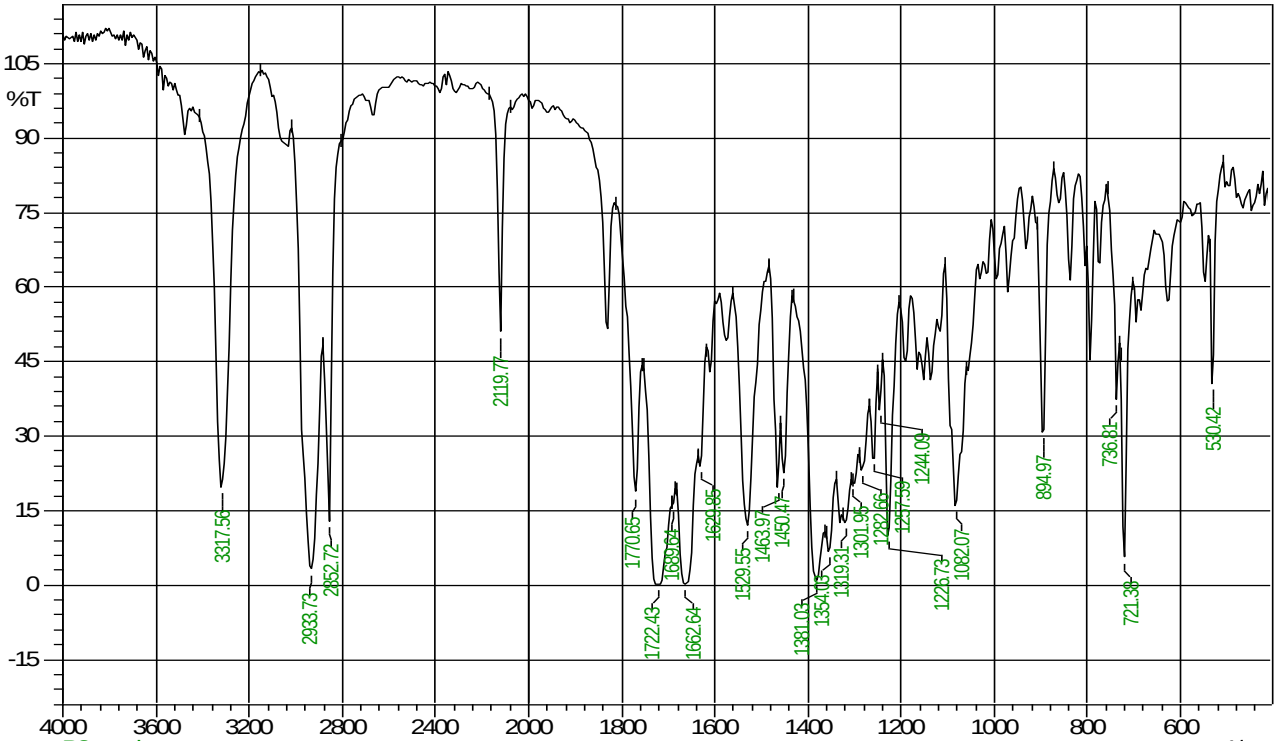

Figure 2: The IR spectrum of Compound (2)

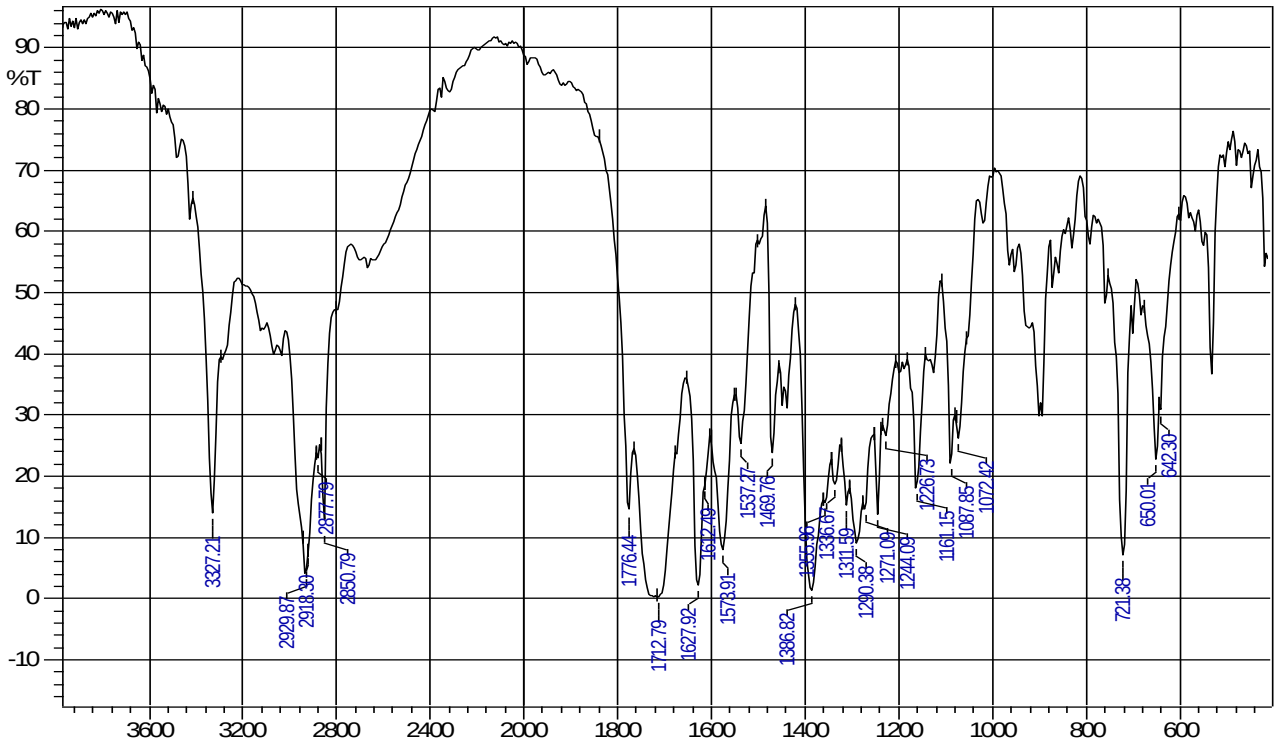

Figure 3: The IR spectrum of Compound (6)

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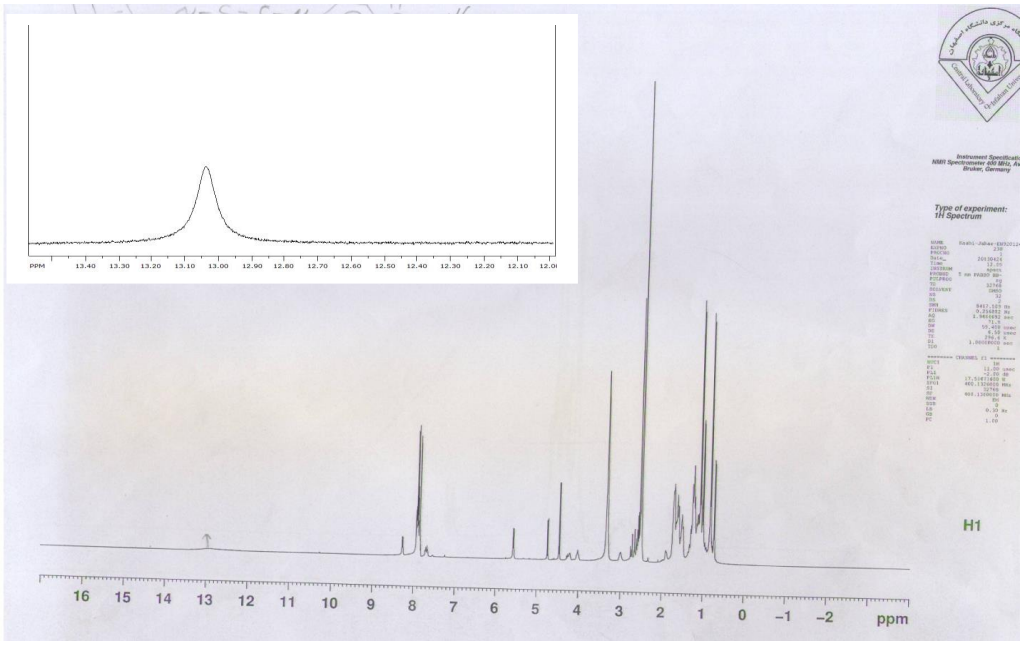
^{1}H–NMR Spectra

The ^{1}H-NMR spectral data of the compounds are given in Table 3. In the ^{1}H-NMR spectrum of compounds the methyl protons appears at δ1.1 ppm and2.3 ppm respectively the CH proton signal as multiplets at δ2.4 ppm. Compound3 show a signal of CH_2atδ 1.0 ppmand a signal of CH_3 proton appears as quartet atδ0.9 ppm and the signal of CH at δ4.4 ppm. All compounds show signals atδ10ppm which may to NH proton of $NHCOC_6H_5$ moiety [15,16,17] and a signal in the range δ 7.5 – 7.85 ppm due to aromatic protons .

s = singlet, d = doublet, m = multiplet, t = triplet, q = quartet, br = broad

Compound	Chemical shifts (ppm)
1	2.4(m,H, -CH(CH_3), 4.5(d,H, -CH-CO), 2.3(S,3H,CH_3CO),1.1(m6H,2CH_3,7.4-7.8(m,Ar-H),10.1(S,H,$NHCOC_6H_5$).
2	2.37(m,H, -CHCCH_3)2,4.4(d,H, -CHCO),2.3(S,3H,OH_3CO)1.1(m,6H,2CH_3),7.66-8.3)(m.Ar-H),10(S,H,$NHCOC_6H_5$)
3	2.3(m,H,-CH(CH_3)$_2$),4.4(S,H, -CHCO),2.2(S,3H,CH_3CO),1.3(t,3H,CH_2CH_3), 0,98(q,2H,CH_2CH_3),7.68-7.83(m,Ar-H),9.98(S,H,$NHCOC_6H_5$)
4	2.6(m, H,-CH(CH_3)$_2$, 1(d, 6H(CH_3)$_2$, 4.5(d, H(-CH-CH(CH_3)$_2$, 7.5-7.8(m, Ar-H), 7.5(br,2H,NH_2),12(br, H, NH-C=O)
5	2.5(m, H,-CH(CH_3)$_2$, 1.1(d,6H(CH_3)$_2$, 4.4(d,H(-CH-CH(CH_3)$_2$,7.6-7.8(m,Ar-H), 7.8(br,2H,NH_2),12.9(br, H, NH-C=O)
6	2.6(m, H,-CH(CH_3)C_2H_5) , 1.0(t, 3H(CH_3CH_2-), 1.3(q, 2H, - CH_2CH_3), 4.5(d, H, -HC-CH(CH_3)C_2H_5), 7.6-7.8 (m, Ar-H),8(br, 2H,NH_2), .2(br, H, NH-C=O)



^{1}H NMR spectrum of Compound (1)

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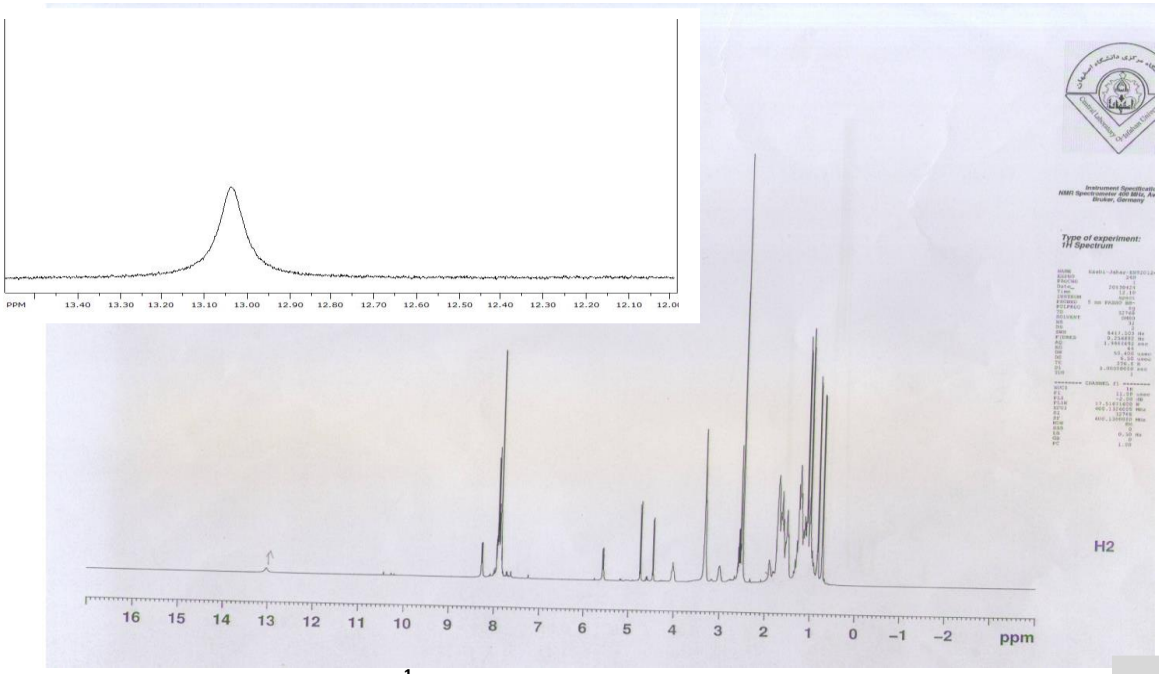
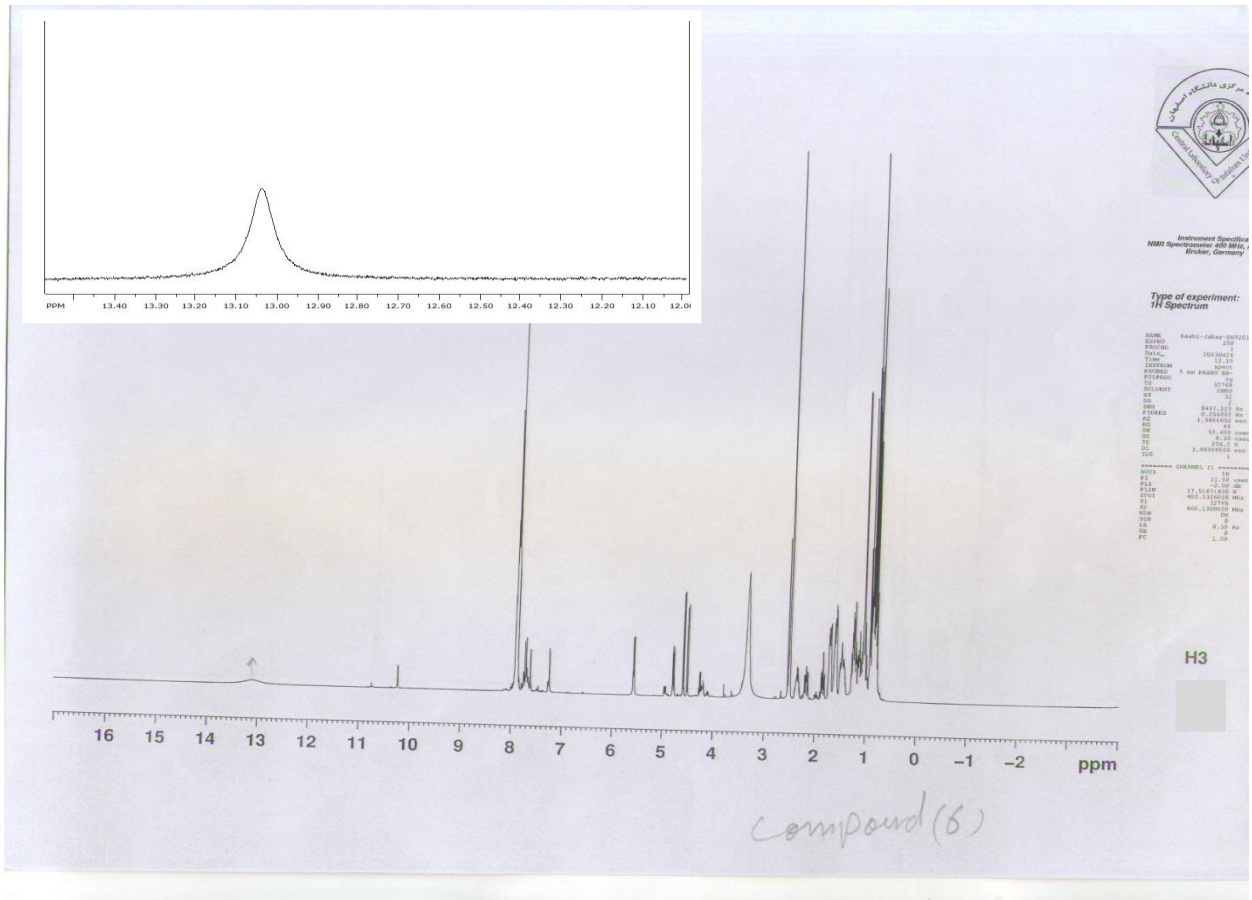


^{1}H NMR spectrum of Compound (2)



^{1}H NMR spectrum of Compound (3)

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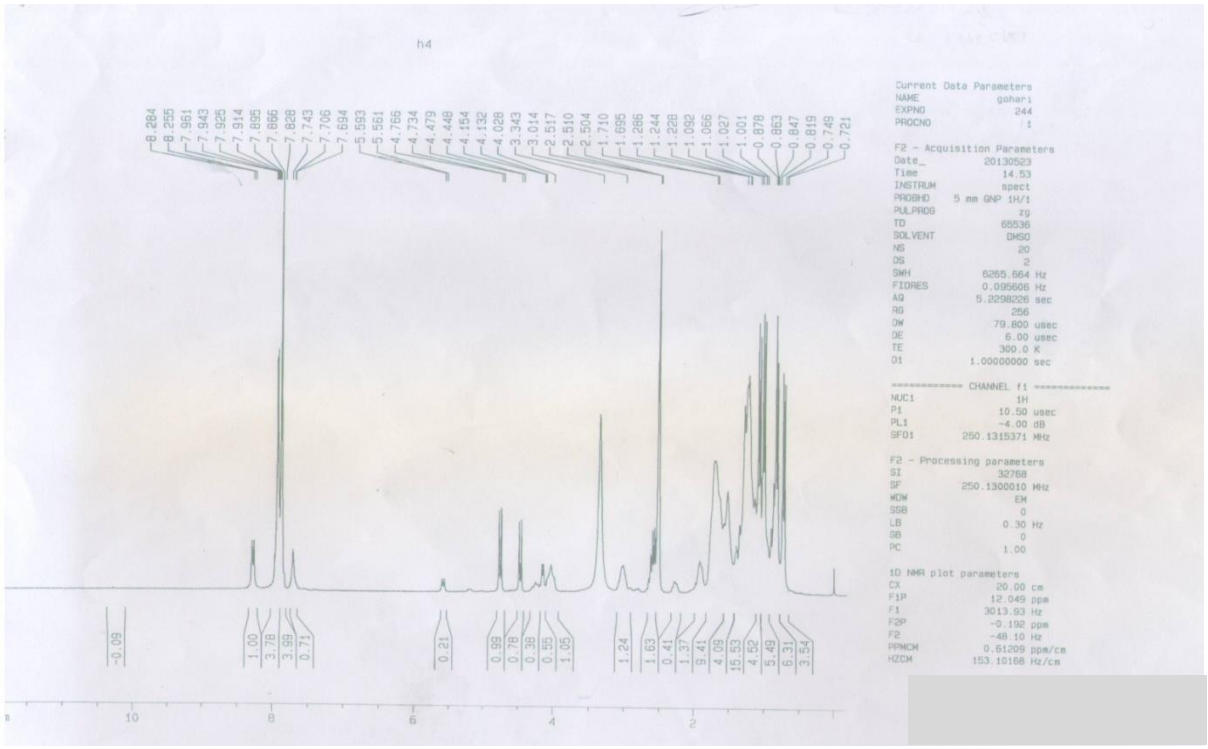
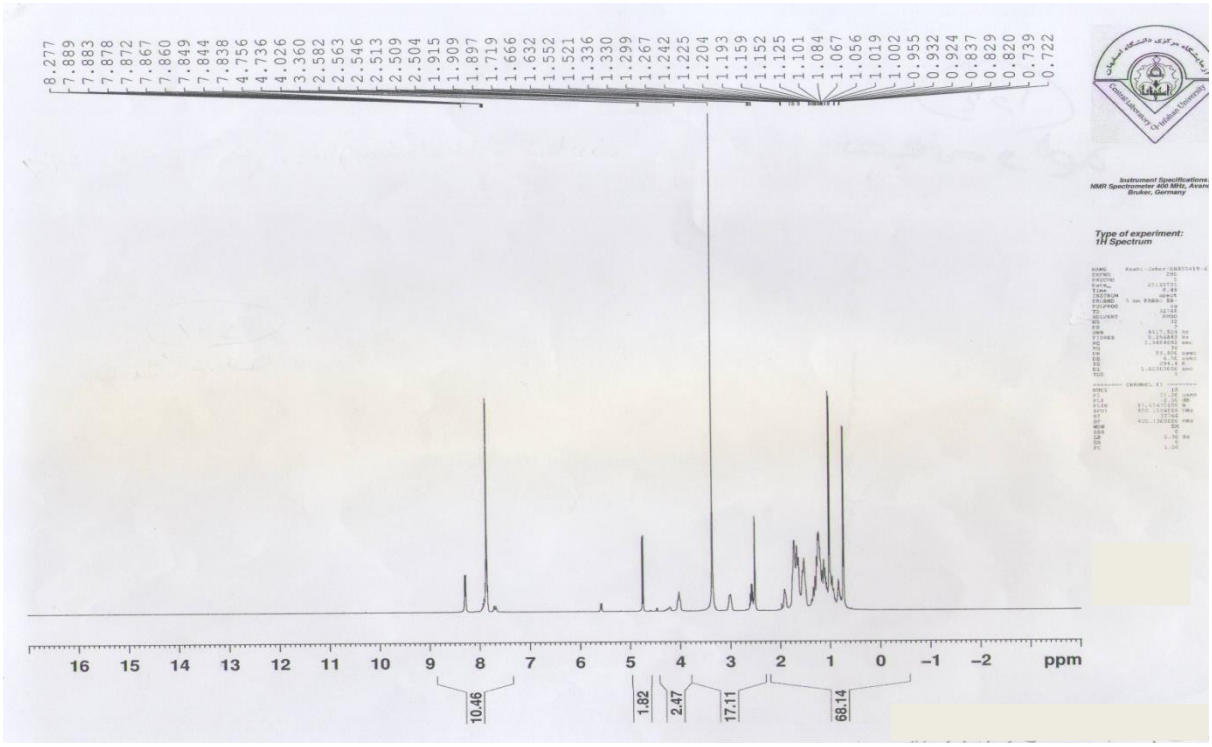


^{1}H NMR spectrum of Compound (4)



^{1}H NMR spectrum of Compound (5)

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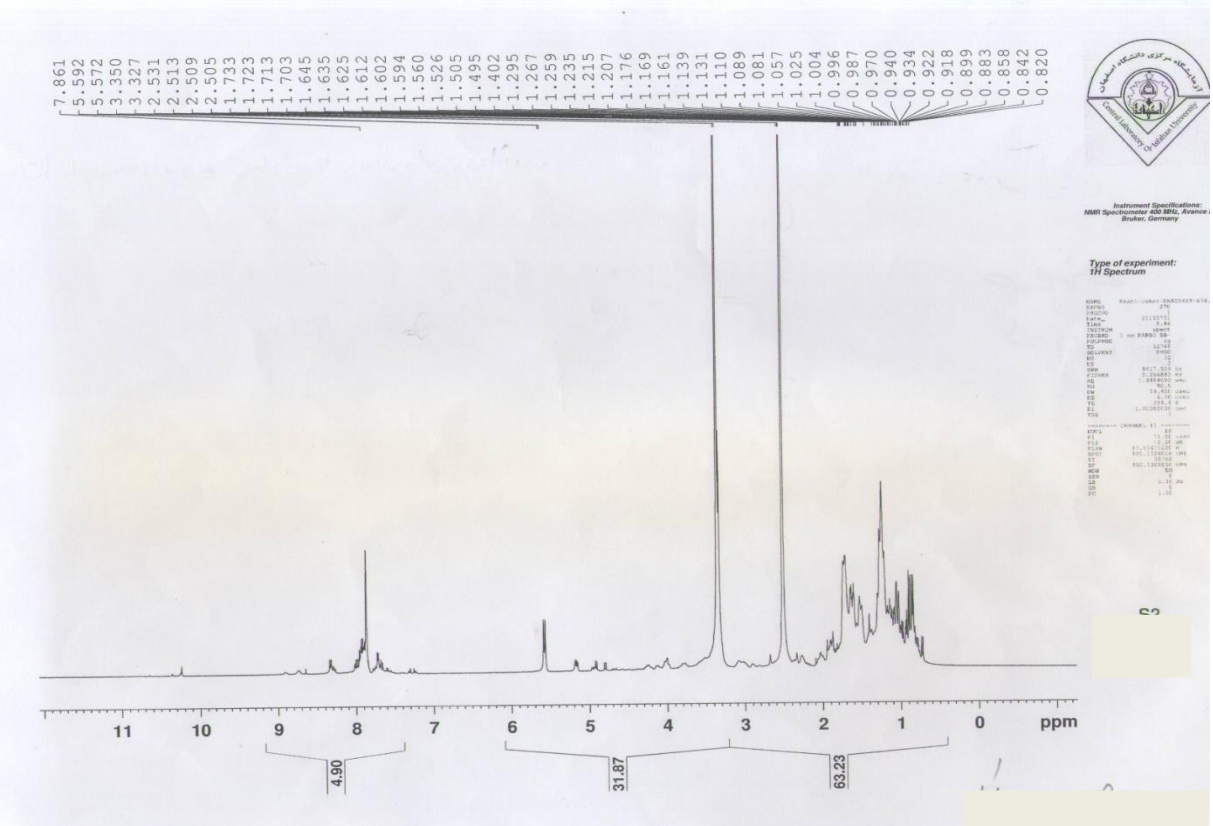

^{1}H NMR spectrum of Compound (6)

Antibacterial study

Sulfa acetamide originally had a wide range of activity, but this range has now been restricted by acquired bacterial resistance and it is not true only for sulfa acetamide rather all the other antimicrobials are becoming. These results are in confirmation with the reports of [19- 24], that *Staphylococcus aureus*is sensitive to sulfa acetamidealone as well as in combination with trimethoprim and other combinations.

The present study indicated thatsulfa acetamide isnot effective against clinical isolate of *Escherichia coli* while it is stilleffective against clinical isolate of *Staphylococcusaureus*Table 3 . The ophthalmicsolution and suspension of sulfa acetamide andin combinations can be used for the treatmentof eye infections caused by *Staphylococcusaureus*, which is very common [19].

Table 3: The anti bacterial activity of the prepared sulfaagainst pathogenic (G+) and (G-) bacterial strains:

Compound	*S. aureus* (Pathogenic)	*E. coli* (Pathogenic)
1	**10**	**R**
2	**12**	**R**
3	**20**	**R**

R = Resistance

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