Synthesis of Novel Heterocyclic Compounds via Schiff bases

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Abstract

In the present study a series of some four-,five-and seven-membered heterocyclic compounds have been synthesized by the reaetion of Schiff bases (1a,b) with chloroacetyl chloride, sodium azide, thioglycolic acid or various anhydrides to give azetidinone (2a,b), tetrazole (3a,b), thiazolidinone (4a,b) and 1,3-oxazepine derivatives (5-8a,b) respectively.

Schiff bases (1a,b)were prepared from the reaction of p-toluidine with aromatic aldehydes. All synthesized compounds were characterized by physical properties and spectral data.

Key words:- Azetidinone, Tetrazole, Thiazolidinone, 1,3-Oxazepine .

الخلاصة

حضر في هذا البحث بعض من مركبات حلقية غير متجانسة حاوية على حلقة رباعية وخماسية وسباعية من مفاعلة قواعد شف (1a,b) مع كلورواسيتايل كلورايد أو ثايوكلايكولك اسيد أو انهدريدات متنوعة للحصول على مشتقات ازيتيدينون (2a,b) وتيترازول (3a,b) وثايوزوليدينون (4a,b) و 3,1–اوكسازبين (5–8a,b) على التوالي .

حضرت قواعد شف (1a,b) من تفاعل بارا– تولويدين مع الديهايدات اروماتية ، شخصت جميع المركبات المحضرة بالطرق الفيزيائية والطيفية .

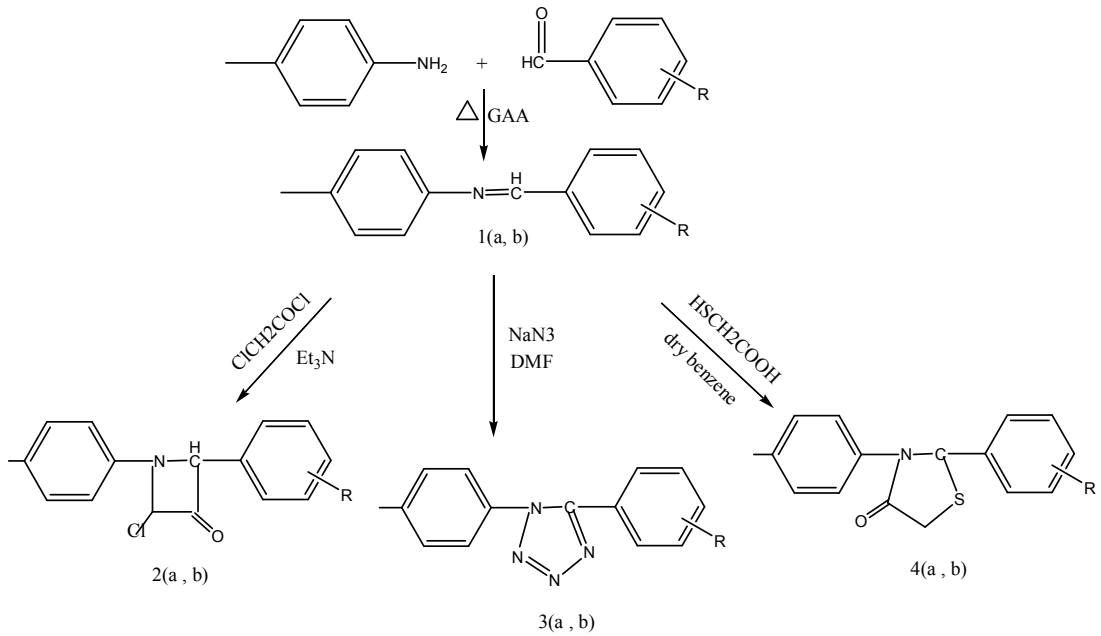
الكلمات المفتاحية :– الازيتيدينون، التترازول، الثايوزولدينون، 3,1 – اوكسازبين .

Introduction

Heterocyclic compounds consisting of four -, five- and seven-membered rings have gaiven more importance in the recent decades for industrial and medicinal reasons. Azetidinone derivatives are one of these compounds , they represent an important class of four –membered cyclic amides, commonly known as β-lactam, due to their antibacterial [1-4], antifungal [2-4], antitubercular [3-4], antianthelminic [5] and enzymetic activity [6], furthermore they found to inhibit cholesterol absorption [7]. Five membered hetercyclics like tetrazole and thiazolidinone derivatives have gained increasing according to their industrial and biological properties. Tetrazole, for example, is well known to have antibacterial, anti-inflammatory [8-10] and fungicide [11] activities. They also have been examined for reducing uric acid [12] , Moreover , tetrazole derivatives are used to prepare epoxy resin which is a raw material of printed circuit boards [13]. On the other hand thiazolidinone are obriously important because of their wide use in medicaments as antihyperglycemic [14] , antitumor growth [15,16] , antifungal [17] , anticonvulsant [18] and inhipitor for CDC7 protein kinase agents [19]. Finally, 1,3-oxazepine ring which constitutes a class of nitrogen and oxygen containing seven-membered heterocyclics have been investigated for their antibacterial activity [20-21] and some of those derivatives show liquid crystalilline properties [22], while others are used as photo stabilizing additives for pmma films [23].

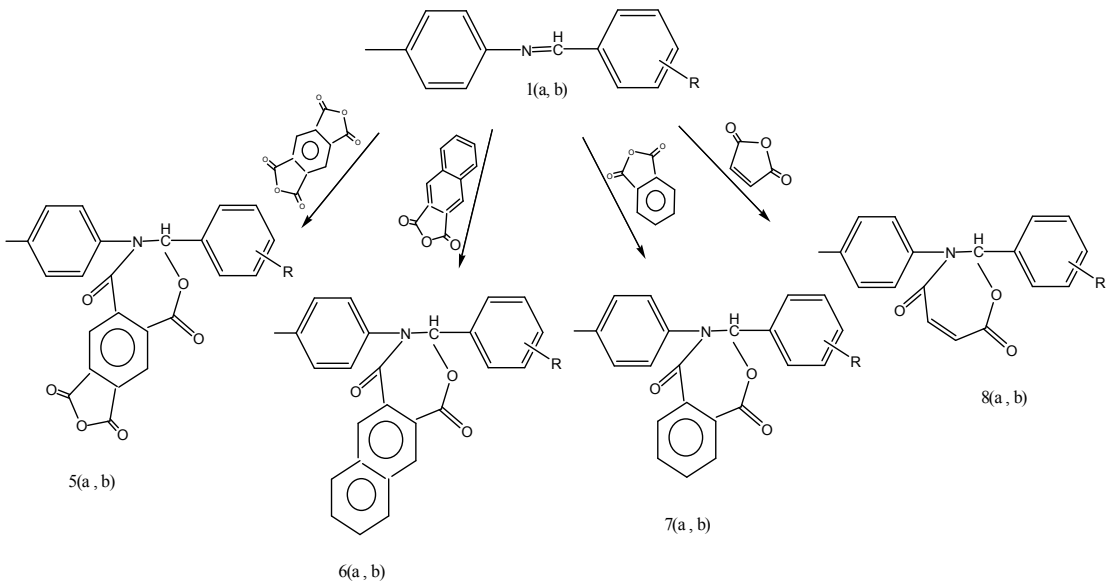
Materials and Methods

All chemicals were supplied from Merck, Fluka and Sigma - Aldrich chemicals Co. and used as received . Melting points were determind in open caoillary tubes on adigital Gallen –Kamp MFB-595 . FTIR spectra were taken on a 8400s Shimadzu spectrophotometer, using samples in KBr disks. ^{1}HNMR spectra were carried out by company : Bruker , model: ultra shield 300 MHz , origin : Switzerland and are reported in ppm(δ), DMSO was used as a solvent with TMS as an internal standard.



1a R =4-N(CH_3)$_2$, 1b R=4- OH

Scheme (1)



1a R =4-N(CH_3)$_2$, 1b R=4- OH

Scheme (2)

Synthesis Methods

Preparation of of Schiff bases (1a,b) :-

Amixture of p-toluidine (0.01mol) and 4-*N,N*-dimethyl benzaldehyde or 4-hydroxybenzaldehyde (0.01mol) were stirred under reflux in absolute ethanol(10 mL) in the presence of few drops of glacial acetic acid for 4hrs . The solvent was evaporated under vacuum and the residue crystallized from ethanol, The solids obtained were filtered ,washed and recrystallized from chloroform, (80% and 72%) , m.p = 111-113 ^{0}C and 194-196^{0}C , respectively.

Synthesis of 3-chloro-2-azetidinone derivatives (2a,b) :-

Chloroacetyl chloride (0.01mol.) in 10mL of dioxan cooled at (0-5) C^o , to this , triethylamine (0.01mol.) in(10mL) dioxane was added , and Schiff bases (0.01mol.) in 10mL of dioxane was slowly added and refluxed in water bath for 12hrs . After the reaction had been completed- (detectad by TLC) , the reaction mixture was poured into ice-cold water to give solid precipitate , which was filtered and dried , recrystallized by benzene:ether(50:50).

Synthesis of tetrazol derivatives (3a,b) :-

Sodium azide (0.01mol) was added to a stirring solution of Schiff bases (1a,b) (0.01mol) in DMF (15mL) , the mixture was refluxed for 4hrs, then it was allowed to cool and the precipitate was filtered , washed with water and recrysallized from petroleum ether.

Synthesis of thiazolidin-4-one derivatives (4a,b) :-

Amixture of Schiff bases (1a,b) (0.01mol) and thioglycolic acid (0.01mol) were stirred under reflux in dry benzene for 8hrs. The solvent was evaporated and the reaction mixture was neutralized with sodium bicarbonate solution , the product was filtered off and recrystallized from chloroform .

Synthesis of 1,3-oxazepine derivatives (5-8a,b) :-

Amixture of equimolar amounts (0.01mol) of Schiff bases (1a,b) and different acid anhydrides in dry benzene (0.01mol) were reflux for 6hrs. The solvent, resulting crystalline solid, was removed and recrystallized from ethanol . All physical properties of compounds were

reported in table (1). All spectral data were reported in table (2).

Results and Discussion:-

The Schiff bases (1a,b) were synthesized by refluxing equemolare amount of p-toluidine with aromatic aldehydes 4-*N,N*-dimethylbenzaldehyde and 4-hydroxybenzaldehyde in dry benzene with some drops of glacial acetic acid (GAA). These Schiff bases were namely *N*-(4-*N,N*-dimethylaminobenzylidene)-4-methylaniline and *N*-(4-hydroxyaminobenzylidene) -2-methylaniline, respectively.

Schiff bases (1a,b) were identified by their melting points and FTIR spectroscopy. FTIR absorption spectra showed the disappearance of absorption bands due to NH_2 and C=O groups of the starting meterials together with appearance of new absorption band in the region (1616-1636) cm^{-1} which is assigned to azomethine group (C=N stretching).

The Schiff bases compounds (1a,b) were treated with chloroacetyl chloride followed by the addition of triethyl amine under reflux in water bath to yield the corresponding azetidinone derivatives (2a,b) , respectively.

The structure of the azetidinone derivatives(2a,b) were identified by their melting point, FTIR and ^{1}HNMR spectroscopy. The FT-IR spectra of compounds (2a,b) showed the appearance of the characteristic absorption band in region (1655-1660) cm^{-1} due to stretching vibration of carbonyl group of azetidine ring. Also the FT-IR spectrum of compound (2b), (Figure 1), showed the suggested band for olefinic (C-H), (C=C) aromatic . All the spectral data for these compounds are listed in (Table 2).

The ^{1}HNMR spectrum of compound (2a), (Figure 2), (in DMSO as a solvent) shows the following signals: The signal at δ 2.33ppm for protons of methyl group, CH proton in azetidione ring appeared as a signal at δ 3.40 ppm, and signal at δ 2.72ppm for six protons for N-$(CH_3)_2$. Furthermore, δ 6.98-8.62 ppm are for aromatic ring protons.

Tetrazole derivatives (3a,b) were obtained by addition of reaction of Schiff bases(1a,b) with sodium azide in dry dimethylformamid (DMF). These compounds were identified by their melting points , FTIR and ^{1}HNMR spectroscopy. The FTIR spectra (Table 2), showed the disappearance of absorption stretching band of imine group with

appearance of new absorption stretching band in the region around 1511cm^{-1} which are assigned to N=N stretching. ^{1}HNMR spectrum of compound (3a) (in DMSO as a solvent), showed many signals(eight aromatic protons) appeared in the region δ 7.02-7.94 ppm and two sharp signals at δ 1.93ppm and δ 3.81ppm could be attributed to protons of -CH_3 group and six protons of N-$(CH_3)_2$ groups, respectively.

The thiazolidine-4-one derivatives (4a,b) were synthesized by refluxing equimolar amounts from the imine compounds with thioglycolic acid in dry benzene .The FT-IR spectra for compound (4a) showed the appearance of the characteristic absorption bands in the region (1605-1730) cm^{-1} due to stretching vibration of carbonyl group of thiazolidinone ring. Also the FT-IR spectrum showed the suggested band for olefinic (C-H) , (C=C) aromatic. All the spectral data for these compounds in table (2). The^{1}H-NMR spectrum for compound (4a) showed the following characteristic chemical shifts , (DMSO)ppm: the aromatic ring protons of compound (4a) appeared as multiplet at δ (6.8-7.8)ppm , singlet signal at δ 2.9 ppm due to CH_3 proton , signal at δ 8.4 ppm due to the C-H proton in thiazolidinone as singlet and protons of CH_2 of thiazolidinone appeared at δ 3.35 ppm . The singlet signal at δ 3.07 ppm is for proton of $(CH_3)_2$N group. It's well known that 1,3-oxazepine-4,7-dione is a seven-member ring containing nitrogen, oxygen and two carbonyl groups. In previous work, a series of 1,3-oxazepine derivatives 5-8(a,b) was prepared from substituted imines1(a,b) with different anhydrides: pyromellitic dianhydride, naphthalic, phthalic, maleic anhydride throughout concerted reaction of the type (2+5) cyclization reaction. The structures of the prepared compounds were determined on the basis of their FT-IR ,1H-NMR .

The characteristic FTIR absorption bands of these compounds, Figure (3) for compound (7a), were confirmed from the disappearance of band due to C=N of schiff base and other peaks characterized of cyclic anhydride of the starting materials together; Besides this, the appearance of band at (1749 – 1710) cm^{-1} for carbonyl groups in oxazepine ring. C-H aliphatic band in the region (2983 - 2845)cm^{-1} and bands around (1280 and 1103 cm^{-1}) belong to asymmetric and symmetric (C-O-C) band. All the spectral data of FTIR for other compounds are listed in Table (2). The ^{1}HNMR spectrum of compound (7b), Figure (4) (in DMSO),

also showed a signal at δ2.49ppm that could be attributed to protons of -CH_3 group and singlet signal that could be attributed to the proton of N-CH absorbed at δ 7.13 ppm. Furthermore, the aromatic ring protons appear at the range (δ 6.90-8.48) ppm, and a singlet at 10.36ppm could be attributed to the proton of -OH group.

Table(1)The physical properties of synthesized compounds

Comp. No.	Nomenclature	Molecular Formula	M.P. °C	Yield%	Color
2a	3-chloro-1- (4 – dimethyl aminophenyl) - 4 -(4-methylphenyl) azetidine-2-one	$C_{18}H_{18}N_2OCl$	158-160	78	Yellowish Brown
2b	3-chloro-1- (4–hydroxyphenyl) -4-(4-methyl phenyl) azetidine-2-one	$C_{16}H_{13}NO_2Cl$	180-182	72	Yellow
3a	N- (4–dimethylaminophenyl) - 1 -(4-methylphenyl)-1H- tetrazole-5-yl	$C_{16}H_{17}N_5$	148-150	70	White
3b	N- (4–hydroxyphenyl) - 1 -(4-methylphenyl)-1H-tetrazole-5-yl	$C_{14}H_{12}N_4O$	200-202	68	Pale yellow
4a	N- (4–dimethylaminophenyl) - 1 -(4-methylphenyl) thiazolidine-4-one	$C_{18}H_{20}N_2OS$	121-123	66	Yellow
4b	N- (4–hydroxyphenyl) - 1 -(4-methylphenyl) thiazolidine-4-one	$C_{16}H_{15}NO_2S$	132-135	68	Bright Brown
5a	Benzene1,2,4,5-{2- (4–dimethylaminophenyl) - 1 –tolyl -2,3- dihydro [1,3]-oxazepine-4,7-diones}	$C_{26}H_{20}N_2O_6$	239-240	76	Dark yellow
5b	Benzene1,2,4,5-{2- (4–hydroxyphenyl) - 1 –tolyl -2,3- dihydro [1,3]-oxazepine-4,7-diones}	$C_{24}H_{15}NO_7$	222-224	80	Orange
6a	2- (4–dimethylaminophenyl) - 1 –tolyl-2,3-dihydrobenz- [1,2e][1,3]-oxazepine-4,7-diones	$C_{28}H_{24}N_2O_3$	166-168	74	Yellowish Brown
6b	2- (4–hydroxyphenyl) - 1 –tolyl-2,3-dihydrobenz- [1,2e][1,3]-oxazepine-4,7-diones	$C_{26}H_{19}NO_4$	205-207	70	Pale Brown
7a	2- (4–dimethylaminophenyl) - 1 –tolyl-2,3-dihydro naphtha- [2,3e][1,3]-oxazepine-4,7-diones	$C_{24}H_{22}N_2O_3$	160-162	72	Dark yellow
7b	2- (4–hydroxyphenyl) - 1 –tolyl-2,3- dihydro naphtha- [2,3e][1,3]-oxazepine-4,7-diones	$C_{22}H_{17}NO_4$	250-252	77	Pale orange
8a	2- (4–dimethylaminophenyl) - 1 –tolyl-2,3-dihydro- [1,3]-oxazepine-4,7-diones	$C_{20}H_{20}N_2O_3$	183-185	72	Off-white
8b	2- (4–hydroxyphenyl) - 1 –tolyl-2,3- dihydro-[1,3]-oxazepine-4,7-diones	$C_{18}H_{15}NO_4$	148-150	70	Brown

Table(2) Charcterrisitic FTIR absorption band of compounds 2-8(a,b) (cm^{-1})

Comp. No.	V(C-H) aromatic	V(C-H) Aliphatic	V (C=O	V (C=C) aromatic	Others
2a	3028	2918-2730	1671	1604	C-Cl:838
2b	3027	2917-2734	1657	1603	C-Cl:837 OH:3320
3a	3026	2909-2793	-	1606	N=N:1515
3b	3028	2918-2795	-	1602	N=N:1511 OH:3249
4a	3039	2924-2733	1719	1602	-
4b	3045	2920-2698	1730	1598	OH:3340
5a	3032	2942-2867	1699	1602	
5b	3041	2974-2789	1715	1608	OH:3398
6a	3098	2922-2735	1700	1601	-
6b	3078	2960-2725	1701	1595	OH:3286
7a	3085	2995-2730	1745	1604	-
7b	3044	2920-2733	1735	1606	OH:3345
8a	3080	2996-2880	1742	1604	-
8b	3079	2958-2715	1659	1602	OH:3356

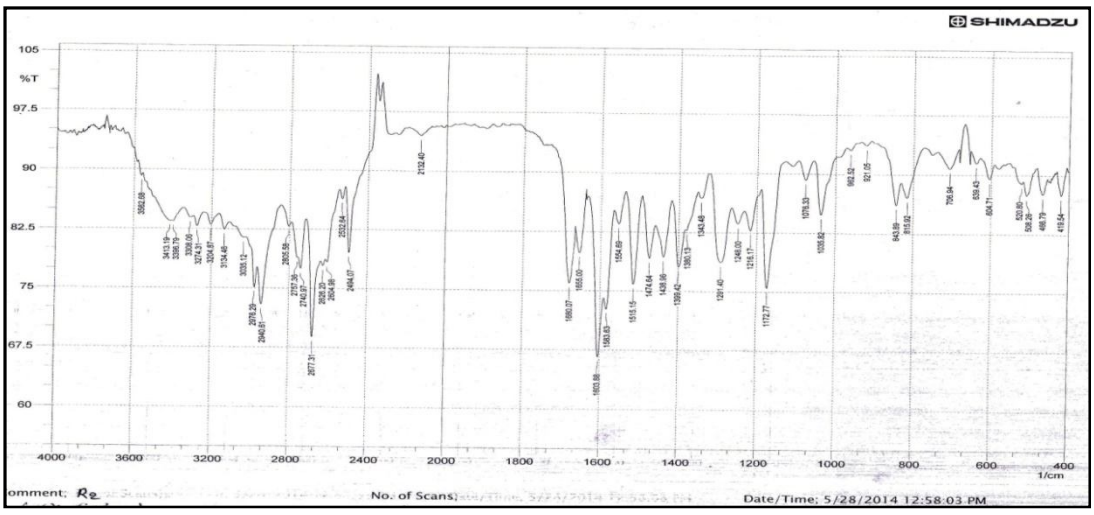


Figure (1): FTIR spectrum of compound (2b)

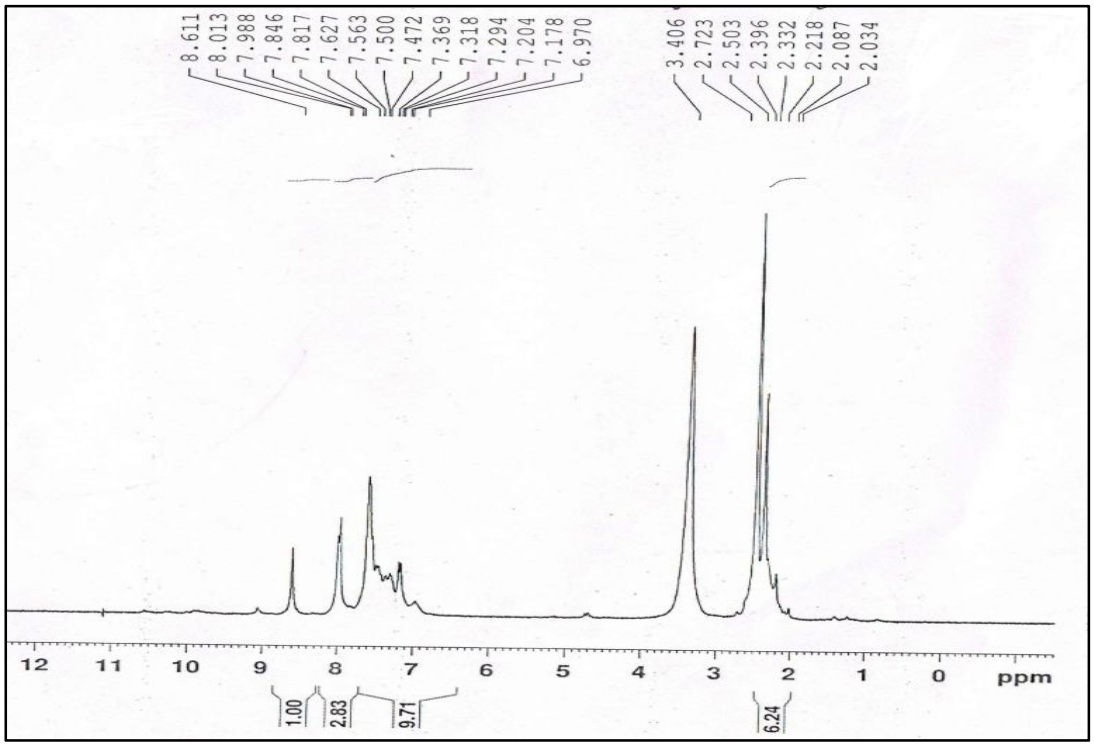


Figure (2):[1]HNMR spectrum of compound(2a)

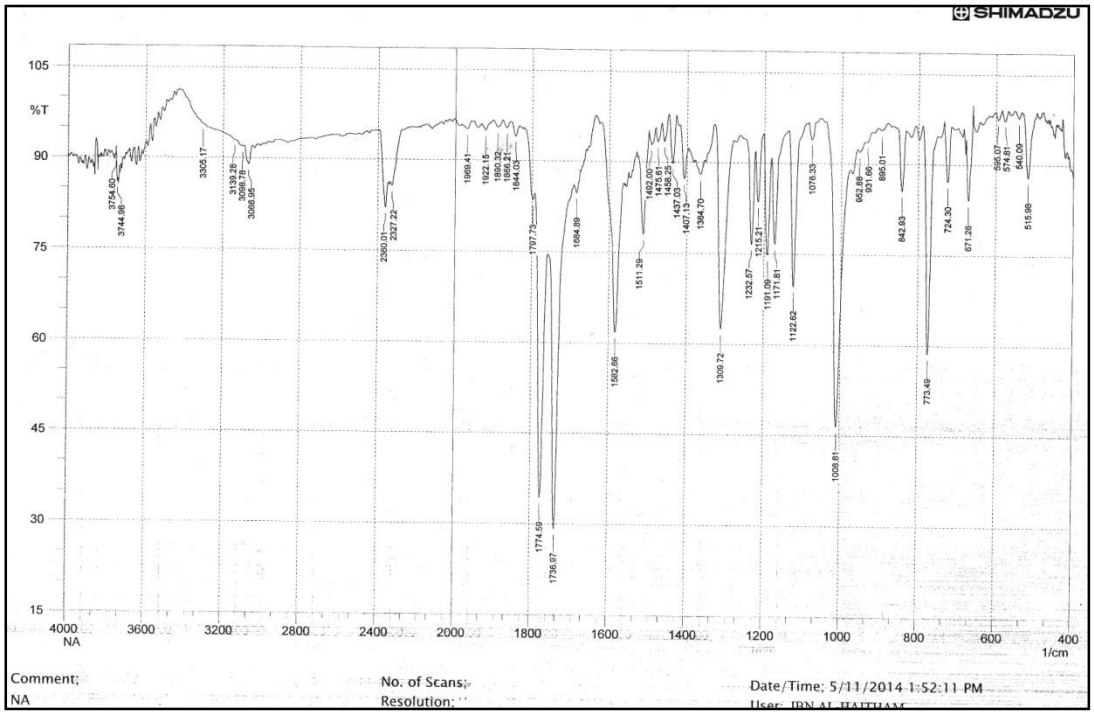


Figure (3): FTIR spectrum of compound (7a)

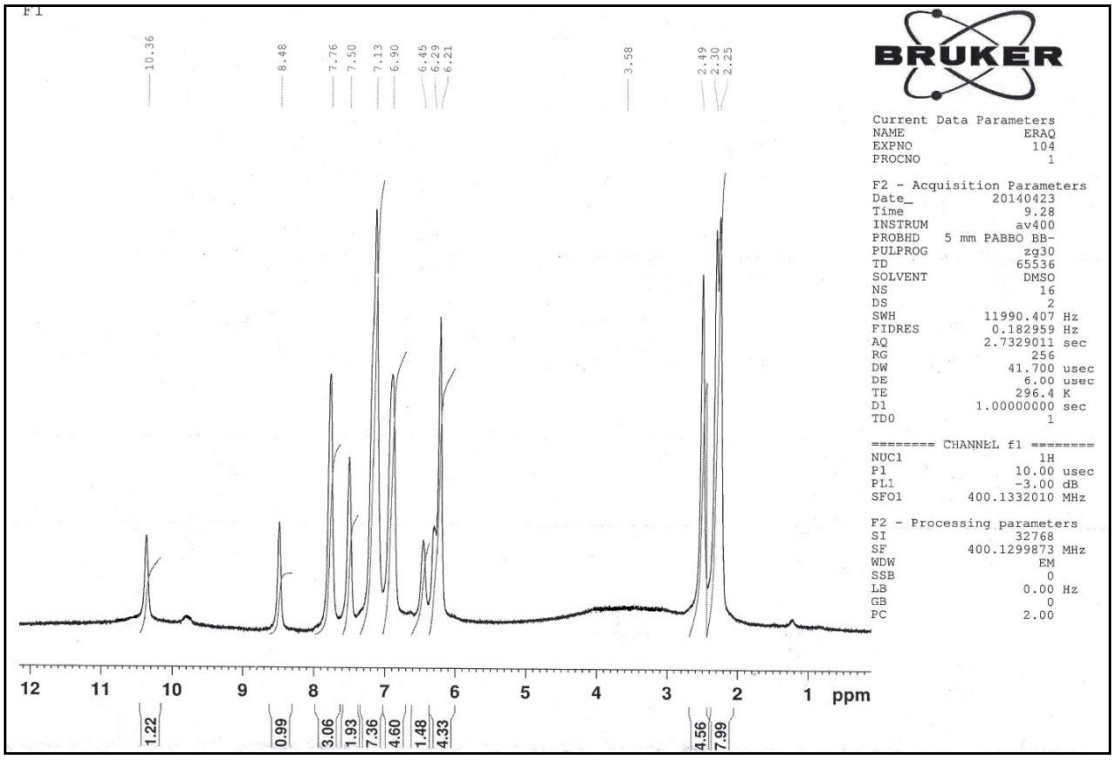


Figure (4):[1]HNMR spectrum of compound(7b)

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