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Synthesis of Some Benzofuran-based Pyrazoline, Isoxazoline, Pyrmidine, Cyclohexenone and Indazole Derivatives

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Abstract:

In the present study benzofuran based chalcones 1(a,b) are synthesized by condensing aromatic aldehydes with 2-acetylbenzofuran in the presence suitable base. These chalcones are very useful precursors for the synthesis of pyrazoline, isoxazoline, pyrmidine, cyclohexenone and indazole derivatives. All these compounds are characterized by their melting points, FTIR and ^{1}HMNR (for some of them) spectral data .

Key words: Pyrazoline, Isoxazoline, Pyrmidine, Cyclohexenone, Indazole.

تحضير بعض مشتقات البايروزولين والايزوكسازولين والبريمد ين والسايكلوهكسينون والاندازول مستندة من البنزوفيوران

هدى احمد حسن

قسم الكيمياء – كلية التربية للعلوم الصرفة / ابن الهيثم – جامعة بغداد.

الخلاصة

في هذا البحث الحالي تم تحضير الجالكونات 1(a,b) من مشتق البنزوفيوران من تكاثف الالديهايدات الاروماتية مع ٢- استيل بنزوفيوران في وسط قاعدي مناسب . استعملت هذه الجالكونات كمادة اولية للحصول على مشتقات البايروزولين ، الايزوكسازولين ، والبريميدين ، والسايكلوهكسينون ، والاندازول . وشخصت جميع المركبات عن طريق قياس درجات اانصهارها والطرائق الطيفية مثل طيف الاشعة تحت الحمراء والرنين النووي المغناطيسي (للبعض منها).

الكلمات المفتاحية : بايروزولين , ايزوكسازولين , بريمد ين , سايكلوهكسينون والاندازول.

Introduction:

Benzofuran ring is the core structure of a lot of unique pharmacophores, their derivatives have been widely used in medicine [1, 2], while chalcones are generic term for the compounds bearing the 1,3-diphenyl-propene-1-one framework. They are very useful intermediates for the synthesis of five-,six- and fused ring heterocyclic compounds The biological activity for chalcones and their hetero-analogous are wide ranging in the recent years, pyrazolines, for example, known to treat hypertension[3]and disorders caused by obesity, diabetes, inflammatory, cardiometabolic and /or cancers [4,5] while isoxazolines are considered biologically active molecules since they are used in controlling parasite infections in humans [6] and animals [7] in addition to their use as insecticides [8]. Pyrmidine derivatives constitute a unique class of two-nitrogen six-membered heterocycles due to their application in medicinal chemistry as antimicrobial [9], anti-cancer [10] and therapeutic agents for the treatment of central nervous system disorders [11]. In addition, chalcones are remarkable precursors for the synthesis of fused-

heterocycles like 2H-indazoles via diaryl-cyclohexenone derivatives. The anti-inflammatory and anti-cancer activities of indazoles were also reported [12-14]. Hence, it appeared of interest to prepare the mentioned heterocycles linked to benzofurn moiety.

Experimental:

A- **Materials:** All chemicals used were supplied from Fluka, BDH, Aldrich and used without further purification.

B- **Instrumentation:** Melting points were taken using electrothermal digital melting point apparatus and they are uncorrected. Infrared spectra were recorded as KBr discs on SHIMADZU-FT-IR-8400 spectro -photometer. H^1NMR spectra were carried out on Bruker Ultra Sheild AMX-300 MHz spectrophotometer, origin : Switzerland and are reported in ppm(δ) in DMSO, using TMS as an internal standard. Measurements were made at chemistry department, Al-albyat university in Jordan .

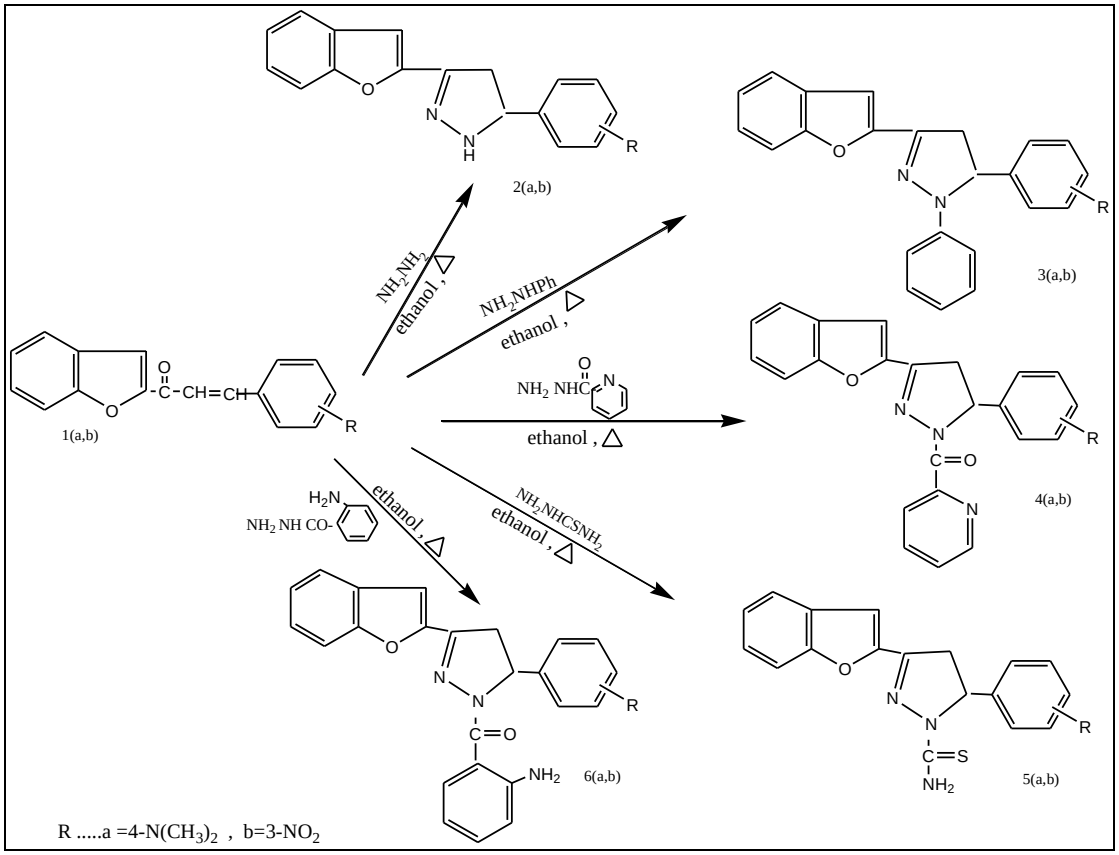
General Synthetic Procedures:

Synthesis of chalcones 1-(Benzofuran-2-yl)-3-(substituted phenyl) prop-2-ene-1-one (1a,b) [2]

A mixture of aromatic benzaldehyde (0.01 mol) and 2-acetyl bezofuran (0.01 mol, 1.60 g) was dissolved in (10 mL) of ethanol, an aqueous soudium hydroxide solution (5 mL, 25%) was added. The mixture was stirred for 2-3h at room temperature. Then it was diluted with ice-cold distilled water (40 mL), filtered, washed well with cold water, dried in air and recrystallized from ethanol to give the required product (1a,b).

Preparation of 3-(Benzofuran-2-yl) Pyrazoline derivatives 2-6(a,b)[5]

A mixture of chalcone 1(a,b) (0.01 mol, 2.91g) and hydrazine hydrate 99% (10mL, 0.01 mol) or substituted hydrazine hydrate (0.01 mol) in absolute ethanol (20 mL) containing glacial acetic acid (1 mL) was refluxed for 4h. After cooling, the solid formed was filtered off, air dried and recrystallized form absolute ethanol .



The scheme (1) for synthesized compounds $1_{(a,b)}$-$6_{(a,b)}$

Preparation of 3-(Benzofuran-2-yl)isoxazoline derivatives 7(a,b)[7]

To a mixture of chalcone (0.01 mol, 2.91 g) and hydroxyl amine hydrochloride (0.01mol, 0.69g), absolute ethanol (50mL), aqueous sodium hydroxide (10%, 6mL) were added, then the reaction of mixture was heated under reflux for 7h and poured slowly into ice cold water and the product obtained was washed with water and recrystallized from absolute ethanol.

Preparation of Pyrimidinone derivatives 8 (a,b)[9]

To a solution of (0.01 mol, 2.91 g) of chalcone, absolute ethanol (10 mL), urea (0.01 mol, 0.6 g) of aqueous sodium hydroxide (10mL, 10 %) were added. The reaction of mixture was heated under reflux for 5h and poured in ice-cold water. The product obtained was filtered washed with water and recrystallized from absolute ethanol.

Preparation of Pyrimidinethion derivatives 9(a,b)[9]

To a solution of chalcone (0.01 mol) absolute ethanol (10 mL), thiourea (0.01 mol, 0.6 g) and aqueous sodium hydroxide (10 mL, 20.0 mmol) were added. The reaction of mixture was heated under reflux for 7h and poured into ice cold water the product obtained was filtered, washed with water and recrystallized from absolute ethanol .

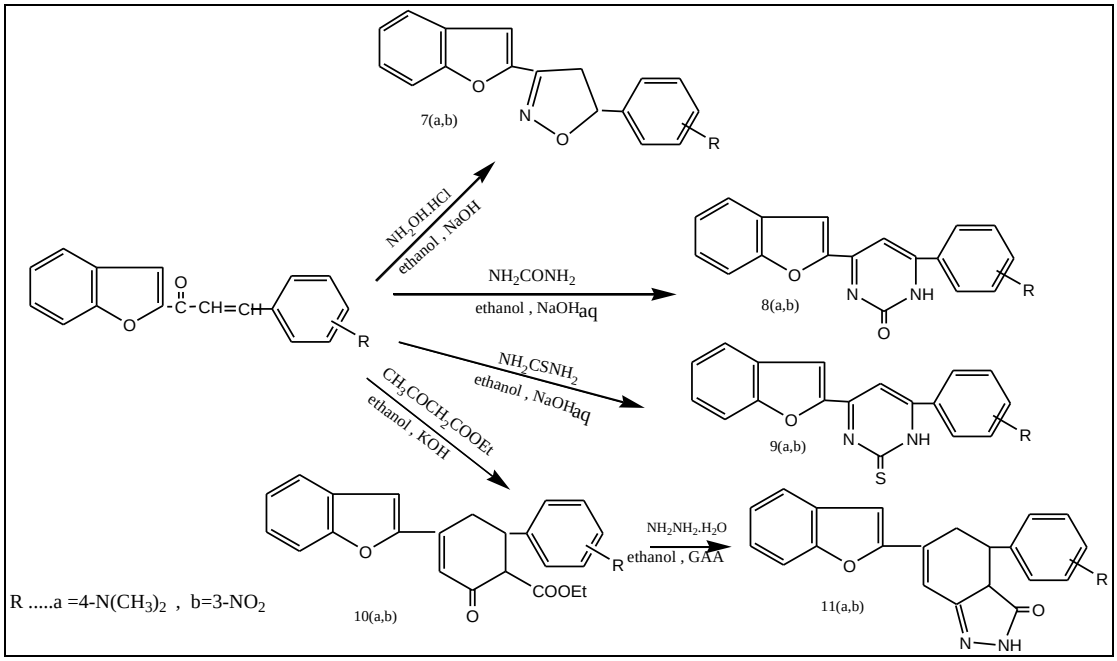
Preparation of Cyclohexanone derivatives 10(a,b) [13]

A mixture of chalcones (1a,b) (0.01 mol) and ethyl acetoacetate (1.30mL, 0.01mol) in absolute ethanol (10mL) containing aqueous potassium hydroxide solution (1 mL, 10%) was refluxed for 5h and then left overnight at room temperature. The solid formed was filtered off, air was dried and recrystallized form absolute ethanol.

Preparation of Indazole derivatives 11(a,b) [13]

A mixture of compounds10(a,b) (0.01 mol) and hydrazine hydrate 99% (5mL, 0.01 mol)in absolute ethanol (10 mL) containing glacial acetic acid (0.5 mL) was refluxed for 2h. After cooling, the solid formed was filtered off, air was dried and recrystallized form chloroform.

The physical data of all synthesized compoundes are listed in Table 1.



The scheme (2) for synthesized compounds $7_{(a,b)}$-$11_{(a,b)}$

RESULTS AND DISCUSSION

The synthesis of chalcones, pyrazoline, isoxazoline, pyrimidinon, pyrimidinthion, cyclohexanone and Indazole derivatives were performed as shown in scheme (1) and (2).

The starting chalcones, namely 1-(benzofuran-2-yl)-3-(4-N,N-dimethylaminophenyl) prop-2-ene-1-one (1a) and 1-(benzofuran-2-yl)-3-(3-nitrophenyl) prop-2-ene-1-one (1b), were synthesized via the Claisen-Schmidt reaction of 2-acetyl benzofuran with 4-N,N- dimethylamino -benzaldehyde and 3- nitrobenzaldehyde, respectively, in ethanol and in the presence of aqueous sodium hydroxide at room temperature. The solids obtained were filtered ,washed and recrystallized from ethanol. The structural assignments of the chalcones 1(a,b) are based on melting points and FTIR spectroscopy [15].

Reaction of chalcones 1 (a,b) with hydrazine hydrate, phenyl hydrazine, 2-pyridinecarboxylic acid hydrazide, thiosemicarbazide and 2-

aminobenzohydrazide under reflux in the presence of glacial acetic acid to yield the corresponding pyrazoline derivatives 2-6(a,b), respectively.

The structure of the pyrazoline derivatives 2-6(a,b) was identified by their melting point, FTIR and ^{1}HNMR spectroscopy. The FTIR spectra of these compounds showed the disappearce of two absorption bands of the CH=CH and C=O group which appears at (1573-1540)cm^{-1} and (1655- 1666) cm^{-1}, in the chalcone 1(a,b) and appearance of new absorption stretching bands of C=N group, (Figure 1) for compound (4a), (Table 2). ^{1}HNMR spectrum of compound (2b), (Figure 2), (in DMSO as a solvent) shows the following signals: a sharp singlet signal at δ 1.22ppm due to a proton of C-H pyrazoline ring , a sharp signals at δ 1.78ppm could be attributed to two protons of CH_2 group-pyrazoline, a signal in the region δ 7.35ppm for furan ring conjugates with benzene ring, many signals(aromatic protons) appeared in the region δ 7.81-7.95 ppm and a sharp singlet signal at δ 8.25ppm due to a proton of N-H group.

Isoxazoline compounds 7(a,b) were synthesized from the reaction of chalcones 1(a,b) with hydroxylamine hydrochloride in alkaline medium. These compounds7(a,b) were identified by their melting points, FTIR and ^{1}HNMR spectroscopy. The FTIR spectra of isoxazoline 7(a,b) showed the disappearance of two absorption bands of the CH=CH and C=O group in the starting material together with appearance of new absorption bands for C=N group around 1610 cm^{-1}and C-O (cyclic ether) group around 1178 cm^{-1}. The FTIR spectral data for isoxazoline 7(a,b) are listed in Table(2).

^{1}HNMR spectrum of compound (7a), (Figure 3) , (in DMSO as a solvent), showed many signals (aromatic protons) appeared in the region δ 7.04-8.25 ppm and a signal in the region δ 6.78ppm for furan ring

conjugates with benzene ring. The triplet signal at 2.97δ ppm and a doublet signal at δ 3.20ppm are due to one protons C-5 and two proton C-4 in the isoxazoline ring, respectively. Furthermore, a signal at δ 3.11ppm for six protons of $N(CH_3)_2$ group .

The pyrimidinone derivatives 8 (a,b) were synthesized from reaction of chalcone 1(a,b) with urea in basic medium. The structure of the pyrimidinone 8(a,b) characterizied by FTIR spectra, (Figure 4), for compound (8a) showed the disappearance of two absorption bands and appearance of new absorption bands for NH and C=O groups around 3338$cm^{-1}$and 1665cm^{-1}, respectively. The other data of functional groups which are characteristics of these compounds are given in Table 2. ^{1}HNMR spectrum of compound (8a), shows the following signals: a singlet signal one proton of NH group appeared as δ9.66 ppm, eight aromatic protons appeared at δ (7.07-7.91) ppm, a singlet signal at δ 6.78 ppm for furan ring conjugate with benzene ring and a signal in the region δ 2.57ppm for they could be attributed to the one proton of C-5 pyrimidinone and a doublet signal at δ 2.50 ppm due to the proton of C6-pyrimidinone. Also, a signal at δ 3.04ppm is for six protons of $N(CH_3)_2$ group.

Pyrimidinethion derivatives 9(a,b) were synthesized from the reaction of chalcones1(a,b) with thiourea in basic medium .The structure of the compounds 9(a,b) are characterized by FTIR and ^{1}HNMR spectroscopy.The characteristic FTIR adsorption band of pyrimidinethion showed the disappearance of two absorption bands of the CH=CH and C=O groups in the chalcones and appearance of new absorption bands for NH and C=S groups around 3384$cm^{-1}$and 1136cm^{-1}, respectively. The FTIR spectral data of these compounds are shown in Table 2 . ^{1}HNMR spectrum of pyrimidinethion (9b), exhibited eight aromatic protons

appeared at δ 6.90-7.91ppm, a singlet signal at δ6.75ppm for furan ring conjugate with benzene ring, a signals at δ 2.44ppm and δ 1.25 ppm for proton at C-5 and C-6 of pyrimidinethion ring. Also, a singlet at δ 5.59ppm could be attributed to one proton of NH group .

The chalcones 1(a,b) were allowed to react with ethyl acetoacetate (1:1) in the presence of aqueous potassium hydroxide10% to give new cyclohexanone derivatives 10 (a,b). The structure of the cyclohexanone 10(a,b) was identified by their melting point, FTIR spectroscopy. The reaction may have proceeded through condensation between C=O of cyclohexanone and NH_2 of hydrazine, followed by cyclization by losing a molecule of ethanol. The new indazole derivatives 11(a,b) were synthesized by refluxing compounds 10(a,b) and hydrazine in the presence of glacial acetic acid. The structure of indazole 11(a,b) was identified by their melting point, FTIR and ^{1}HNMR spectroscopy. The FTIR spectra of these compounds showed the disappearce of absorption bands and appearance of new absorption bands of NH and C=N group at 3363cm^{-1} and 1603cm^{-1}, respectively. Functional groups which are characteristic of these compounds are given in Table 2. Finally, the ^{1}HNMR spectrum of compound (11b) (in DMSO), shows the following signals: eight aromatic protons appeared in the region δ 7.02-7.94 ppm. a singlet signal at δ 6.78ppm for furan ring conjugates with benzene ring. a signal at δ 3.81 ppm are attributed to cyclohexanone protons . Furthermore, a singlet signal at δ 5.42ppm was assigned to proton of NH .

Table 1: Physical properties of synthesized compounds 2-11(a,b)

Comp. No.	Namecalture	Molecular Formula	M.P ˚C	Yield %	Color
2a	4,5-dihydro-3-(1-benzofuran-2-yl)-5-(4-dimethylaminophenyl) -1H-pyrazole	$C_{19}H_{17}N_3O$	97-99	78	Pale yellow
2b	4,5-dihydro-3-(1-benzofuran-2-yl)-5-(3-nitrophenyl) - 1H- pyrazole	$C_{17}H_{11}N_3O_3$	139-141	72	Dark Yellow
3a	4,5-dihydro- 3-(1-benzofuran-2-yl)-5-(4- dimethylaminophenyl) -1-phenyl-1H- pyrazole	$C_{25}H_{21}N_3O$	195-197	78	Green-yellow
3b	4,5-dihydro-3-(1-benzofuran-2-yl)-5-(3- nitrophenyl) -1-phenyl-1H-pyrazole	$C_{23}H_{15}N_3O_3$	175-177	73	Red
4a	4,5-dihydro-3-(1-benzofuran-2-yl)-5-(4- dimethylaminophenyl) -1 (2-pyridine carboxylic acid) -1H-pyrazole	$C_{23}H_{20}N_4O_2$	124-126	67	Yellowish golden
4b	4,5-dihydro-3-(1-benzofuran-2-yl)-5-(3- nitrophenyl -1 (2- pyridine carboxylic acid)-1H-pyrazole	$C_{21}H_{14}N_4O_4$	70-72	65	Red-brown
5a	4,5-dihydro- 3-(1-benzofuran-2-yl)-5-(4- dimethylamino phenyl) pyrazole-1-carbothioamide	$C_{20}H_{18}N_4O$ S	244-246	71	Orange
5b	4,5-dihydro- 3-(1-benzofuran-2-yl)-5-(3-nitrophenyl) pyrazole-1-carbothioamide	$C_{22}H_{12}N_4O_3S$	228-230	68	Brownish Yellow
6a	4,5-dihydro- 3-(1-benzofuran-2-yl)-5-(4- dimethylaminophenyl) -1(2-aminobenzo) - 1H-pyrazole	$C_{26}H_{22}N_4O_2$	174-176	74	Off-white
6b	4,5-dihydro-3-(1-benzofuran-2-yl)-5-(3-nitrophenyl) -1(2-aminobenzo - 1H- pyrazole	$C_{24}H_{16}N_4O_4$	101-103	64	Pale-orange
7a	3-(1-benzofuran-2-yl)-5-(4-dimethyl aminophenyl)-4,5-dihydroisoxazole	$C_{19}H_{18}N_2O_2$	146-148	63	Yellowish brown
7b	3-(1-benzofuran-2-yl)-5-(3-nitrophenyl)-4,5-dihydroisoxazole	$C_{17}H_{12}N_2O_4$	150-152	66	bright Brown
8a	6-(1-benzofuran-2-yl)-4-(4-dimethyl aminophenyl) pyrimidin -2(1*H*)- one	$C_{20}H_{18}N_3O_2$	111-113	76	Pale yellow
8b	6-(1-benzofuran-2-yl)-4-(3-nitrophenyl) pyrimidin -2(1*H*)- one	$C_{18}H_{12}N_3O_4$	94-96	65	Brownish yellow
9a	6-(1-benzofuran-2-yl)-4-(4-dimethyl aminophenyl) pyrimidine- 2(1*H*)-thione	$C_{20}H_{18}N_3OS$	122-124	73	Yellowish Brown
9b	6-(1-benzofuran-2-yl)-4-(3-nitrophenyl) pyrimidine- 2(1*H*)-thione	$C_{18}H_{12}N_3O_3S$	212-214	60	Light brown
10a	Ethyl-4-(1-benzofuran-2-yl)- 6- (4-dimethylaminophenyl)-2-	$C_{25}H_{24}NO_4$	66-68	78	orange-Yellow

	oxocyclohexa-3-enecarboxylate				
10b	Ethyl-4-(1-benzofuran-2-yl)- 6- (3-nitrophenyl)-2-oxocyclohexa-3-enecarboxylate	$C_{23}H_{18}NO_6$	117-119	68	Pale Brown
11a	4,5-dihydro-4-(4-dimethylaminophenyl)- 6-(1-benzofuran-2-yl)-2H-indazol-3(H)ones	$C_{23}H_{22}N_3O_2$	74-76	63	Light yellow
11b	4,5-dihydro-4-(3-nitrophenyl)- 6-(1-benzofuran-2-yl)-2H-indazol-3(H)ones	$C_{21}H_{16}N_3O_4$	242-244	60	Off-white

Table No.2:Characteristic FTIR absorption bands of synthesized compounds 2-11(a,b)

Comp. No.	v N-H	v C=O	v C=N	v C=C aromatic	v C=S	C-O
2a	3381	-	1630	1585	-	-
2b	3441	-	1622	1554	-	-
3a	-	-	1652	1555	-	-
3b	-	-	1644	1559	-	-
4a	-	1664	1654	1579	-	-
4b	-	1662	1632	1558	-	-
5a	-		1654	1600	1160	-
5b	-		1612	1588	1142	-
6a	-	1665	1614	1552	-	-
6b	-	1670	1640	1545	-	-
7a	-	-	1614	1564	-	1068
7b	-	-	1614	1591	-	1174
8a	3383	1646	1618	1600	-	-
8b	3331	1674	1612	1598	-	-
9a	3384	-	1665	1612	1246	-
9b	3444	-	1660	1555	1257	-
10a	-	1731	-	1604	-	-
10b	-	1743	-	1592	-	-
11a	3363	1709	1602	1520	-	-
11b	3380	1710	1630	1510	-	-

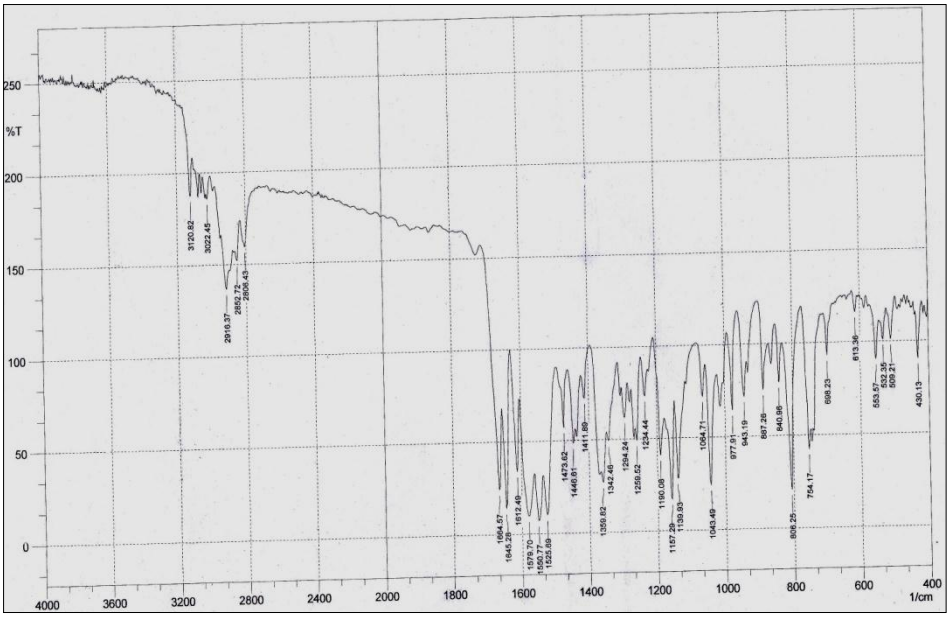


Figure No.(1):FT-IR spectrum of compound (4a)

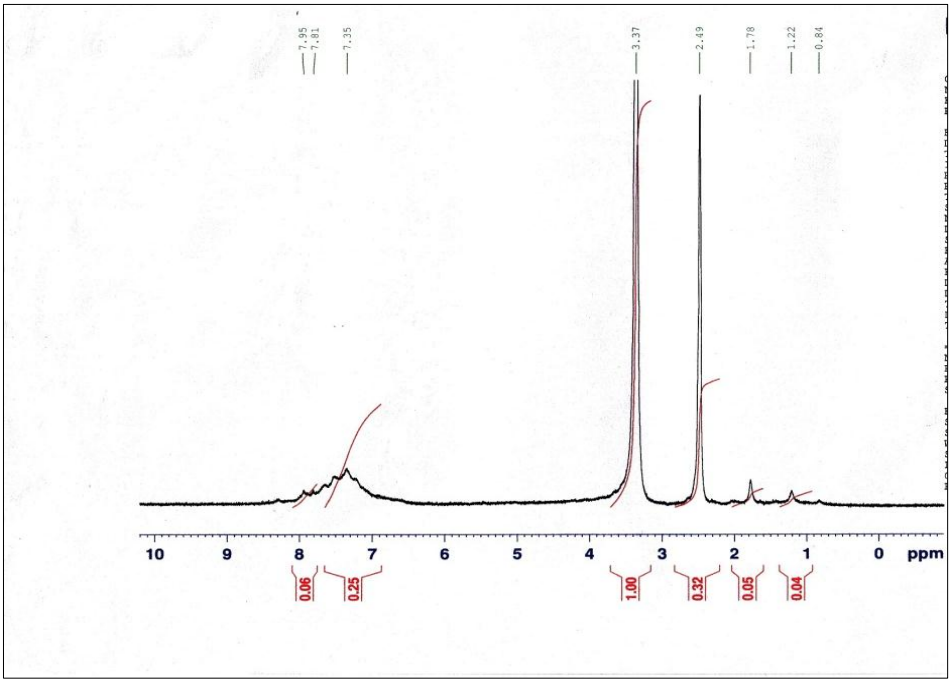


Figure No.(2):^{1}HNMR spectrum of compound (2b)

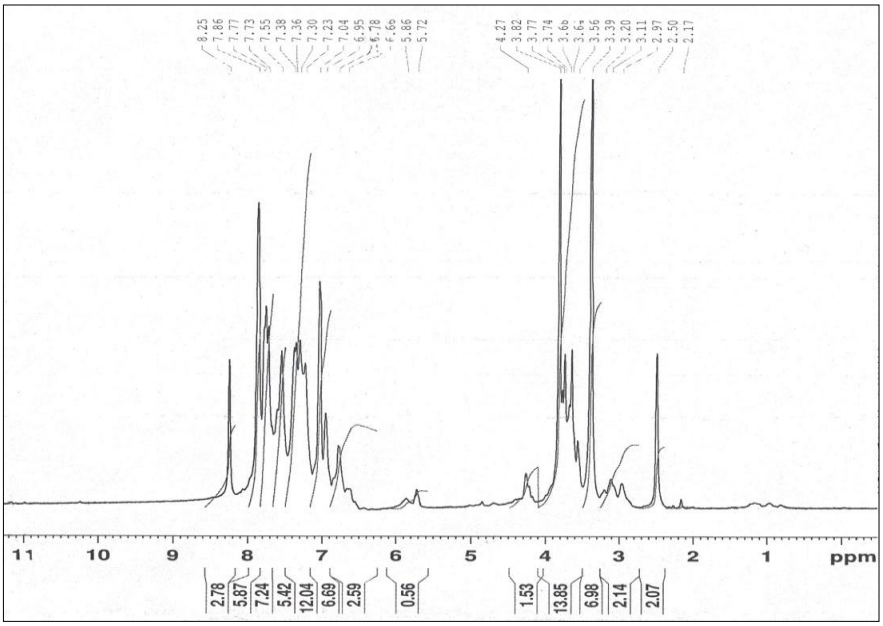


Figure No.(3):[1]HNMR spectrum of compound (7a)

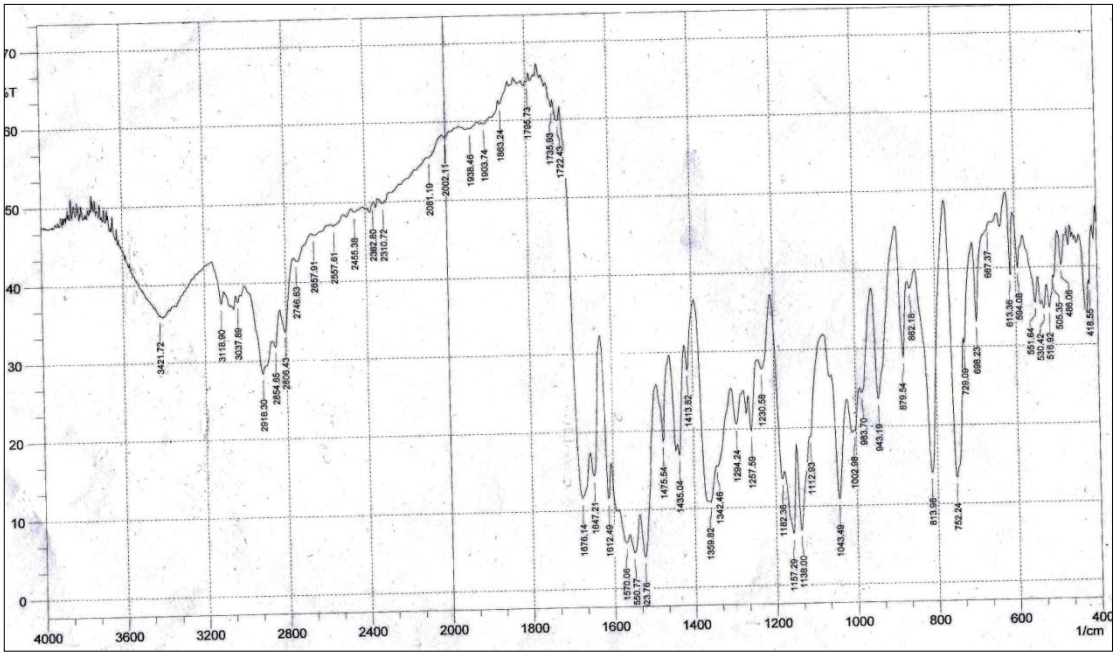


Figure No.(4):[1]HNMR spectrum of compound (8a)

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