Enaam Fadil Mousa et al /J. Pharm. Sci. & Res. Vol. 10(9), 2018, 2297-2304

ISSN:0975-1459
Journal of Pharmaceutical Sciences and Research
www.jpsr.pharmainfo.in

Preparation and Characterization of Oxadiazoles Derived from Ibuprofen

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Abstract

Some new oxadiazoles are prepared by reaction of some hydrazides of different carboxylic acids (aliphatic and aromatic acids) with Ibuprofen in the presence of Phosphorousoxy chloride. The hydrazides are prepared from the reaction of carboxylic acid with thionyl chloride to yield acid chloride and by adding ethanol (absolute) to acid chloride. The product will be an ester and then hydrazine hydrate is added to the ester to produce the hydrazide. The new oxadiazoles compounds are identified by their melting points, FT-IR, ^{1}H-NMR, and mass spectroscopy.

Keywords: Ibuprofen Derivatives, Antiinflammatory, Heterocyclic compounds, Analgesic.

INTRODUCTION

Ibuprofen, (NSAID), is a propionic acid derivative (2-arylpropionic acids; Figure 1). It is almost insoluble in water having a pKa of 5.3 [8].

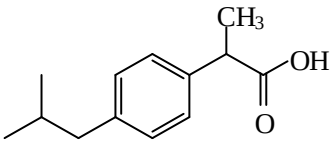


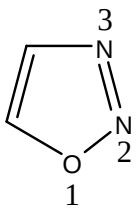
Fig. (1) The structural formula of Ibuprofen

Ibuprofen was introduced for the first time in 1969 as a superior alternative to aspirin [1,2]. Ibuprofen is widely used in clinical medicine for treatment of a number of inflammatory and arthritic diseases [3]. It has effective analgesic, anti-inflammatory and antipyretic actions, but low toxicity [10-14]. Ibuprofen is usually prescribed at a dose of 400-800 mg three imes a day [7].

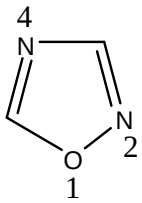
Like other NSAIDs, ibuprofen exerts its pharmacological effects by acting as an inhibitor of Cyclooxygenase (COX) enzyme (it inhibits both COX1 and COX2 isoforms) [16]. This enzyme catalyzes biosynthesis of prostaglandins, the endogenous mediators that play an important role in the production of pain, inflammation and fever [17].

Oxadiazole is one of the heterocyclic compounds that are found as building units within several biological molecules [18]., mostly those having five- and six-membered rings [19]. The synthesis of heterocyclic compounds is because of their wide potential biological and industrial applications [20-24].

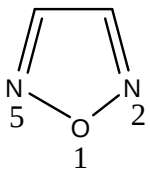
Oxadiazoles are five-membered cyclic compounds with one oxygen and two nitrogen atoms. The oxadiazole ring has four [25] isomers as shown below:



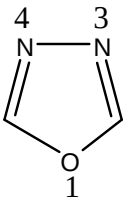
1,2,3-oxadiazole



1,2,4-oxadiazole



1,2,5-oxadiazole



1,3,4-oxadiazole

MATERIALS AND METHODS

1. Instruments

1-Melting points are recorded using hot stage Gallen Kamp melting point apparatus and are uncorrected.

2-Infrared spectra are ecorded using Fourier Transform infrared SHIMADZU (8300) (F.T.IR) infrared spectrophotometer. KBr disc or thin film was performed by College of education for pure sciences Ibn-Al-Haitham, University of Baghdad.

3-Thin-layer chromatography (TLC) was carried out using fertigfolllen precoated sheets type polygram Silg and the plate was developed with iodine vapor.

4-^{1}H-NMR spectra were recorded on Foruier Transform Varian spectromerter, operating at 300 MHz with tetramethylsilane as internal standard in DMSO-d_6, measurements were made at Chemistry Department in Iran.

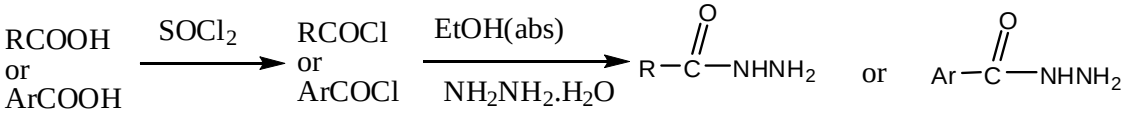
2. Materials

All chemical compounds were obtained from Fluka or Aldrich. Ibuprofen was obtained from Samara Drugs Industry (SDI), Iraq.

The reaction sequence leading to the formation of new compounds is outlined in Scheme1.

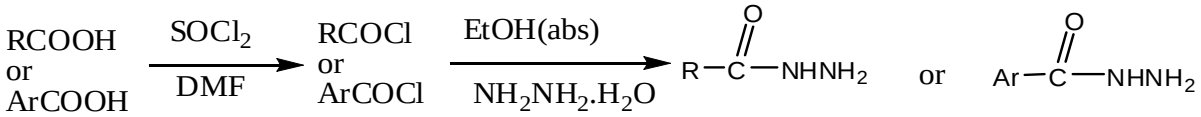
3. Experimental methods

3.1. Preparation of hydrazide compounds (1-9) [26-28]



The hydrazides of some acids such as *p*-nitrobenzoic acid, *O*-chlorobenzoic acid, *m*- nitrobenzoic acid, furoic acid, phenyl acetic acid, cinnamic acid, Terephthalic acid, glutaric acid and *p*- chlorobenzoic acid were prepared from mixing 5 g of acid with 10 ml of thionyl chloride in a round flask and heated to reflux and left to cool for 1.5 h then absolute ethanol (10 ml) was added. After that, hydrazine hydrate (10 ml) was added, the mixture cooled, the solid obtained was filtered and recrystallized from ethanol.

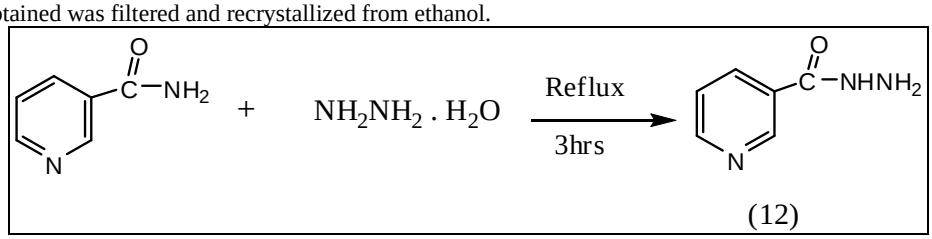
3.2. Preparation of Carboxylic acid hydrazide compounds (10, 11)[29]



The hydrazides of some acids such as quinaldic acid and 3,5-dinitrobenzoic acid were prepared from mixing 5 g of acid with 10 ml thionyl chloride in a round flask and added few drops of dimethyl formamide (DMF) then the mixture was refluxed at for (1.5 hr) and left to cool then added absolute ethanol (10 ml) after that added hydrazine hydrate (10 ml). The mixture was cooled, the solid obtained was filtered and recrystallized from ethanol .

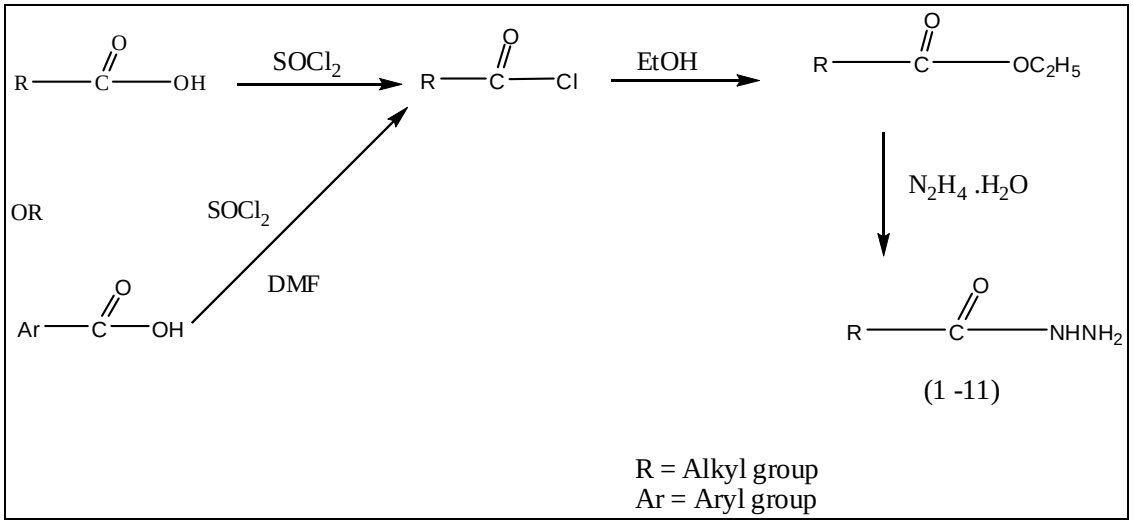
3.3. Preparation of 3-Pyridine carboxylic acid hydrazide (12)

3-Pyridine carboxylic acid hydrazide was prepared from mixing 3-Pyridine carboxylic acid (0.041 mol, 5 g) with 10 ml of hydrazine hydrate. The mixture was refluxed for 3 hrs (checked by TLC). After that, the mixture was evaporated to remove non-reacted hydrazine hydrate, the solid obtained was filtered and recrystallized from ethanol.

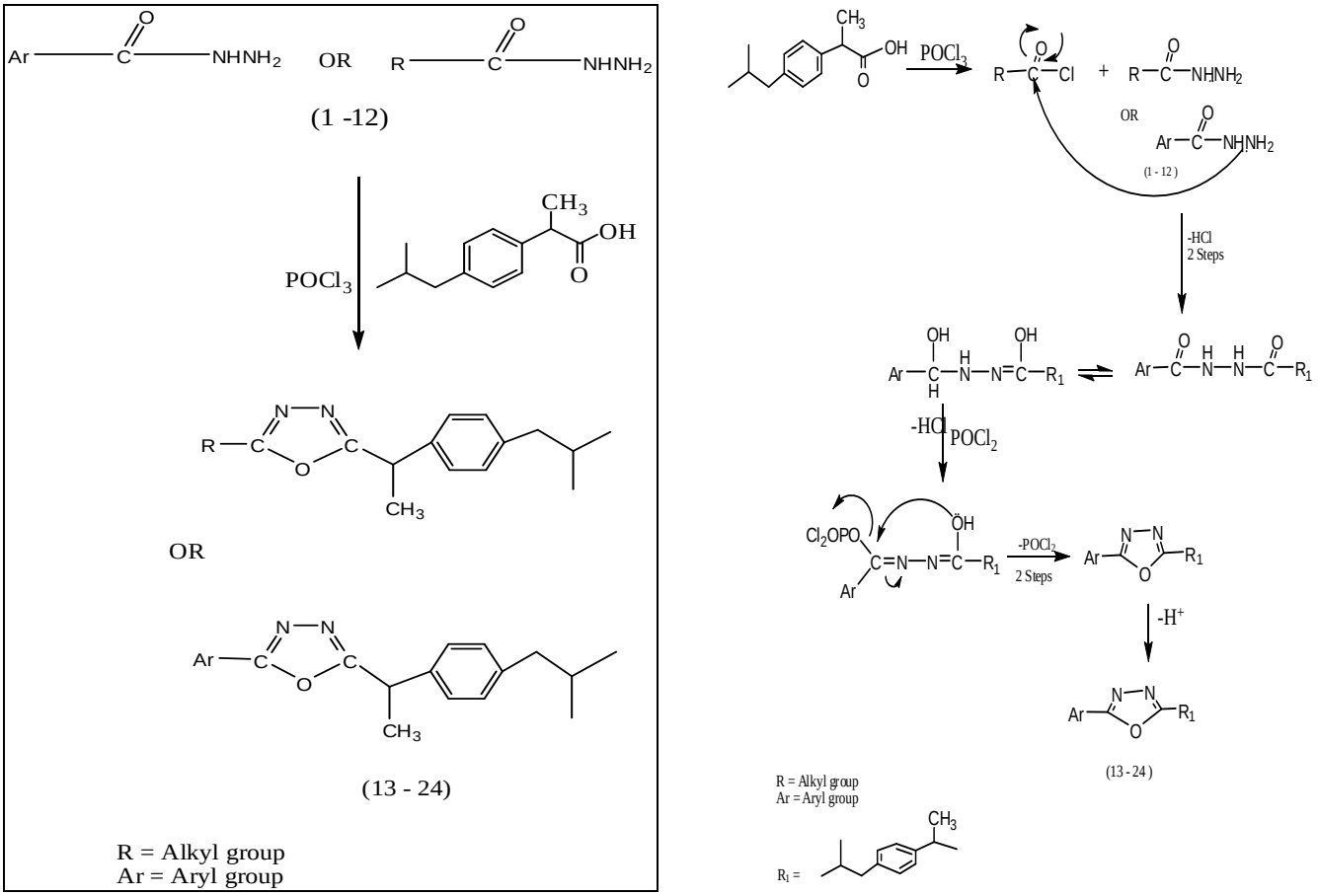


3.4. Synthesis of Oxadiazole Compounds (13-24)

A mixture of each hydrazide derivative (0.002 mole), Ibuprofen (0.002 mole, 0.5 gm), except for terepthalic acid and glutaric acid hydrazides (0.002 mol), Ibuprofen (0.004 mole) and phosphorus oxychloride (10 ml) were refluxed for (21 hrs). After the end of reaction (checked by TLC), the mixture was cooled by addition of ice-water drop-wise (10 ml), the mixture was neutralized by sodium hydroxide to obtain a precipitate which was filtered, dried and recrystallized from ethanol.



Scheme 1: The reaction sequence leading to the formation of new compounds



Scheme 2: Steps for Synthesis Oxadiazole Compounds of Ibuprofen

RESULTS AND DISCUSSION

The oxadiazole compounds (13-24) were synthesized from the reaction of Ibuprofen with hydrazide compounds of different carboxylic acids in presence of phosphorous oxychloride. The mechanism of this reaction [30] is shown below (Scheme 2).

The structures of the produced (13-24) compounds, which are listed in Table (1), were confirmed by their physical properties and by spectral methods such as FT-IR (some of them by ^{1}H- NMR).

FT.IR spectra of the prepared compounds showed characteristic absorption bands at (1542-1649) cm^{-1}, (3015-3057) cm^{-1}, and (2866 -2968) cm^{-1} due to ν(C=N),ν(C-H) aromatic, and ν(C-H) aliphatic of methyl group (Table 2 and Figures 2-5).

The H-NMR spectra of compounds 15 and 24 showed the following characteristics chemical shifts (DMSO as a solvent) were appeared, doublet signal at δ (0.75-0.80, and 0.84-0.86) ppm, respectively, that maybe attributed to the protons of two methyl group of isobutyl. In addition, doublet signal at δ (1.24-1.36 , and 1.31-1.32) ppm, respectively, that could be attributed to the protons of methyl group. Also, doublet signals at δ (7.02 –7.20, and 7.06 –7.24) ppm, respectively, that could be assigned to benzene ring protons, as shown in Figures 6 and 7.

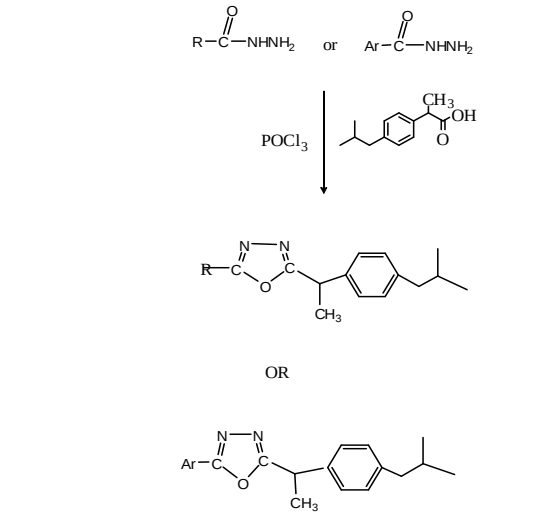
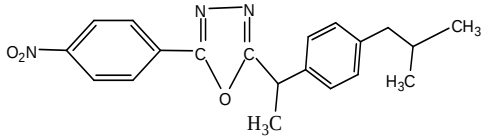
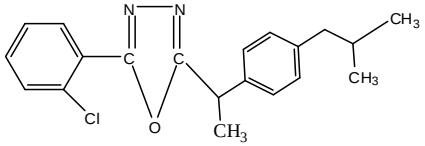
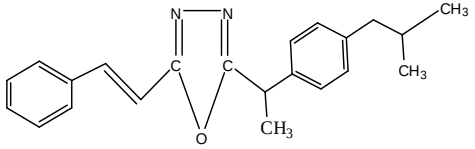
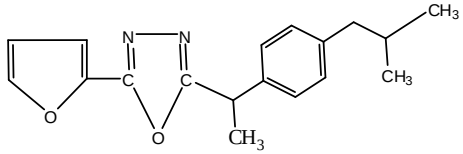
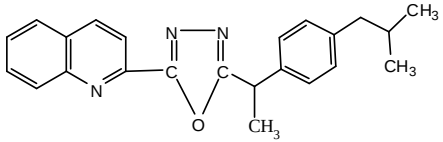
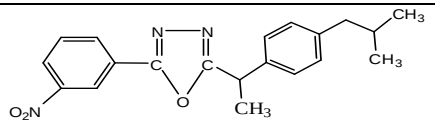
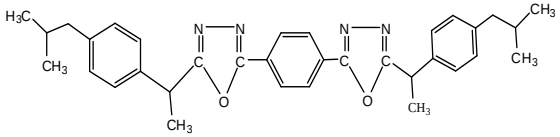
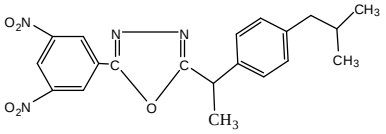
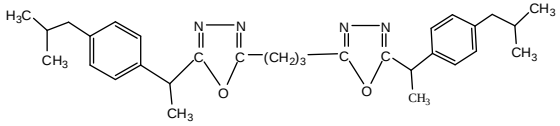
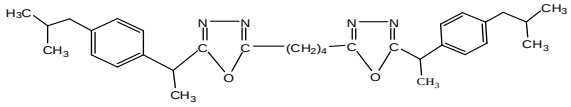
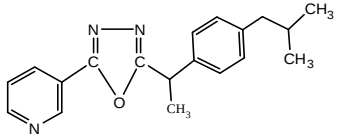
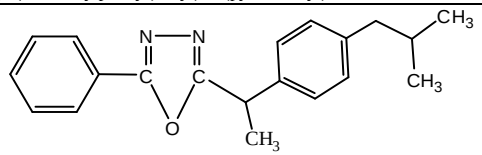


Table (1): The physical properties of oxadiazole compounds (13-24)

Comp. No.	Compound Structure	Molecular Formula	Molecular Weight	Yield %	Melting point °C	Color	R_f
13	 2-(1-(4-isobutylphenyl)ethyl)-5-(4-nitrophenyl)-1,3,4-oxadiazole	351	65	65	>250(d)	orange	0.81
14	 2-(2-chlorophenyl)-5-(1-(4-isobutylphenyl)ethyl)-1,3,4-oxadiazole	$C_{20}H_{21}N_2OCl$	340.5	68	138-140	white	0.86
15	 (*E*)-2-(1-(4-isobutylphenyl)ethyl)-5-styryl-1,3,4-oxadiazole	$C_{22}H_{25}N_2O$	332.16	71	-----	brown	0.83
16	 2-(furan-2-yl)-5-(1-(4-isobutylphenyl)ethyl)-1,3,4-oxadiazole	$C_{18}H_{20}N_2O$	296.o8	73	153-155	yellow	0.86
17	 2-(1-(4-isobutylphenyl)ethyl)-5-(quinolin-2-yl)-1,3,4-oxadiazole	$C_{23}H_{23}N_3O$	357.13	75	147-149	gray	0. 9

18	 2-(1-(4-isobutylphenyl)ethyl)-5-(3-nitrophenyl)-1,3,4-oxadiazole	$C_{20}H_{21}N_3O_3$	351	79	------	brown	0.90
19	 1,4-bis(5-(1-(4-isobutylphenyl)ethyl)-1,3,4-oxadiazol-2-yl)benzene	$C_{34}H_{38}N_4O_2$	534.13	70	150-152	yellow	0.93
20	 2-(3,5-dinitrophenyl)-5-(1-(4-isobutylphenyl)ethyl)-1,3,4-oxadiazole	$C_{20}H_{20}N_4O_5$	396.12	71	158-160	brown	0.87
21	 1,3-bis(5-(1-(4-isobutylphenyl)ethyl)-1,3,4-oxadiazol-2-yl)propane	$C_{31}H_{40}N_4O_2$	500.12	68	178-180	white	0.88
22	 1,4-bis(5-(1-(4-isobutylphenyl)ethyl)-1,3,4-oxadiazol-2-yl)butane	$C_{32}H_{42}N_4O_2$	514.14	77	------	brown	0.83
23	 2-(1-(4-isobutylphenyl)ethyl)-5-(pyridin-3-yl)-1,3,4-oxadiazole	$C_{19}H_{21}N_3O$	307.13	72	236-238	orange	0.73
24	 2-(1-(4-isobutylphenyl)ethyl)-5-phenyl-1,3,4-oxadiazole	$C_{20}H_{22}N_2O$	306	65	204-206	white	0.82

Table(2): The IR characteristic bands of compounds (13-24)

Comp.NO.	ν(C=N)	ν(C- H) Ar.	ν(C-H) Aliph. ν(CH_3)	ν(C-H) Aliph. ν(CH_2)	ν(C-O-C)	Other Bands
13	1606	3015	2956, 2868	2926, 2848	1201-1246, 1010-1070	**ν** (C-NO_2) 854 ν(N-O)1531,1348
14	1595	3022	2953, 2868	2931, 2854	1207-1255, 1051-1072	C-Cl 744
15	1598	3024	2956, 2868	2927, 2854	1201-1282, 1022-1070	-----
16	1600	3018	2955 2868	2925, 2855	1200-1272, 1068	---------
17	1598	3024	2954, 2868	2922, 2850	1201-1258, 1070	--------
18	1604	3057	2968, 2870	2926, 2841	1213-1261, 1047-1076	**ν** (C-NO_2)848 ν(N-O)1504,1346
19	1600	3018	2953, 2866	2926, 2854	1201-1263, 1020-1070	-------
20	1597	3022	2954, 2868	2927, 2848	1201-1276, 1051-1074	**ν** (C-$NO)_2$844 ν(N-O)1541,1344
21	1598	3020	2951, 2895	2926, 2841	1215-1244, 1022-1085	------
22	1645	3020	2953, 2868	2918, 2854	1207-1276, 1066	------
23	1649	3049	2954, 2868	2924, 2845	1207-1249, 1022-1072	------
24	1598	3024	2954, 2866	2923, 2853	1201-1269, 1024-1070	------

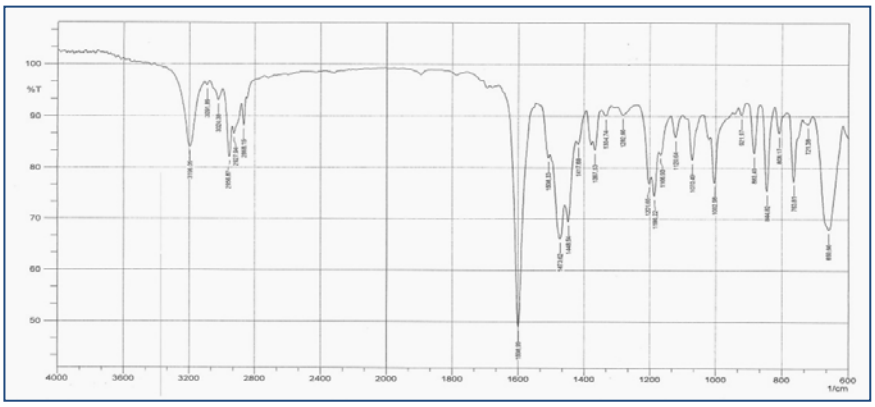


Fig (2): FT-IR Spectrum of compound 15

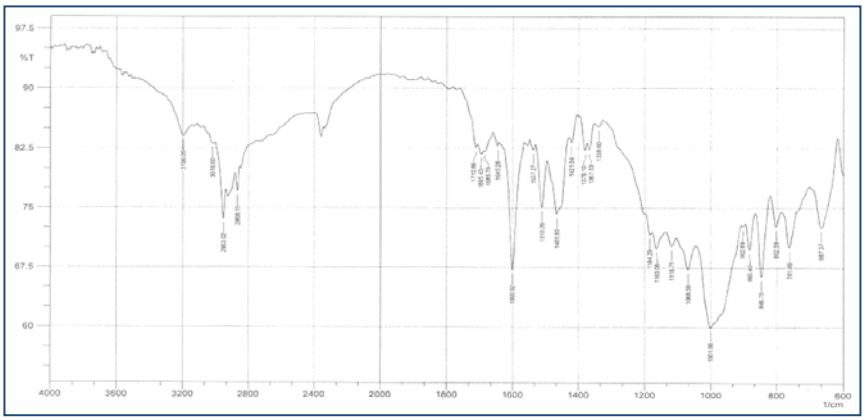


Fig (3): FT-IR Spectrum of compound 16

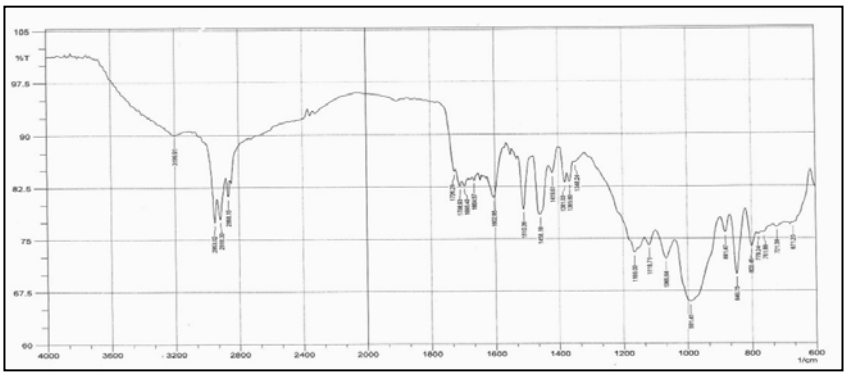


Fig (4): FT-IR Spectrum of compound 17

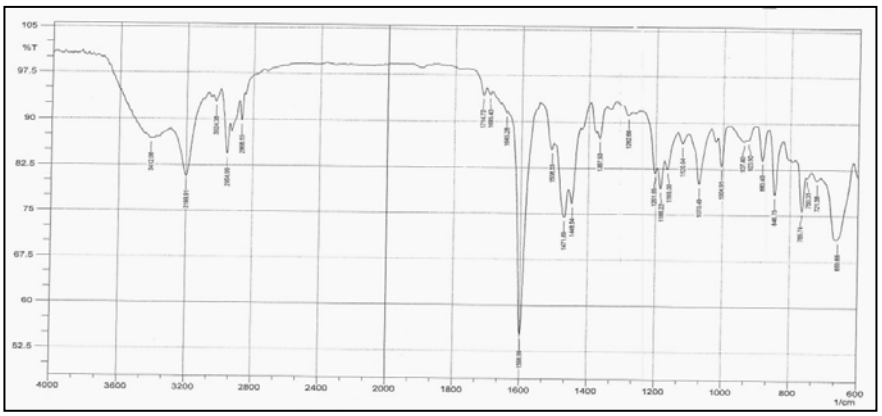


Fig (5): FT-IR Spectrum of compound 22

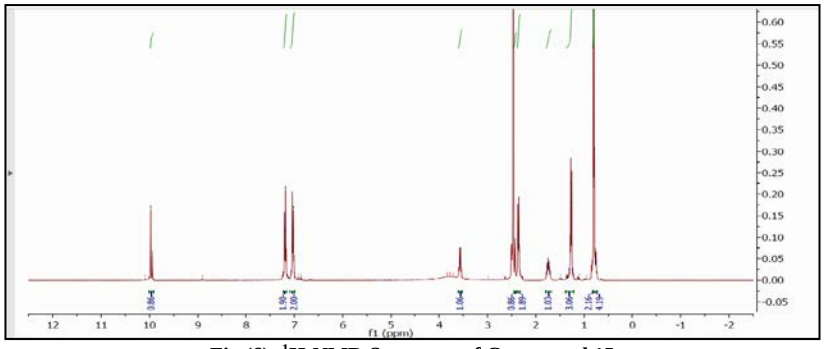


Fig (6): ^{1}H-NMR Spectrum of Compound 15

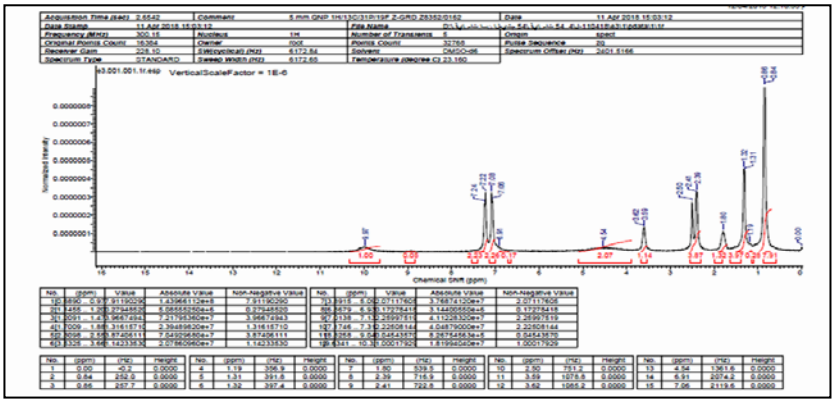


Fig (7): ^{1}H-NMR Spectrum of Compound 24

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