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Synthesis and Characterization of Oxadiazole compounds derived from Naproxen

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Abstract

Some new oxadiazole compounds were prepared by the reaction of some hydrazides of different carboxylic acides (aliphatic and aromatic acids) with Naproxen in presence of phosphorous oxy chloride ($POCl_3$). There are several methods are available for the synthesis of hydrazide derivatives , the most important one is based on the reaction of esters with hydrazine monohydrate that has been applicated in this research for preparation hydrazide derivatives . These synthezied oxadiazole compounds were identified by melting points, FT-IR , and H-NMR , spectroscopy.

Keywords: Naproxen, Naproxen Derivatives , Anti inflammatory

1- INTRODUCTION

Naproxen ((S)-(+)-2-(6-methoxy-2-naphthyl) propionic acid) is a non-steroidal anti- inflammatory drug (NSAIDs) derived from propionic acid [1]. Naproxen is widely used in therapeutics as analgesic and antipyretic and it is also used for relief of symptoms of rheumatoid arthritis and osteoarthritis in addition to treatment of dysmenorrheal, among other indications [2] .

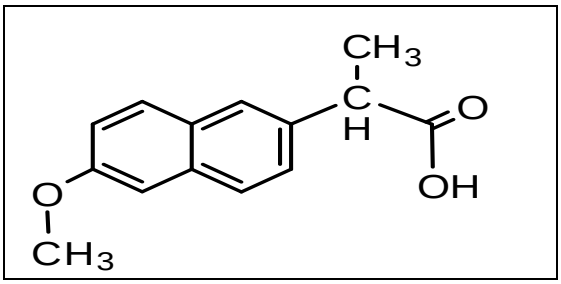
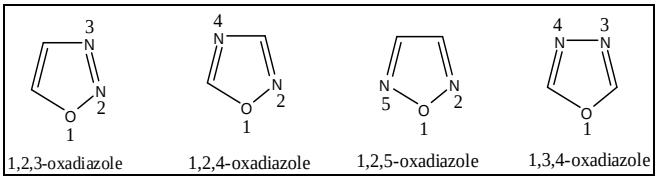


Fig.(1) The Structure of Naproxen

Oxadiazole is one of heterocyclic compounds that are found as construction units through several biological molecules [8], mostly are molecules which contain five and six membered ring [9]. The synthesis of heterocyclic compounds is due to potential biological and industrial applications [10-14]. The heterocyclic compounds showed a wide range of pharmacological properties as antibacterial [15], antiviral [16] and anti-inflammatory agent [17], also, heterocyclic compounds play an important role in biochemical process [18] because the side groups of the most typical and essential constituents of living cells are based on aromatic heterocyclic compounds. Between them, sulfur and nitrogen containing heterocyclic compounds have maintained the interest of researchers through the development of organic synthesis [19].

Oxadiazoles are five-membered ring compounds with three atoms one oxygen atom and two nitrogen atoms. The oxadiazole ring has four[20] isomers as shown below:



2-MATERIALS AND METHODS

A- Instrumentals

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

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

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

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.

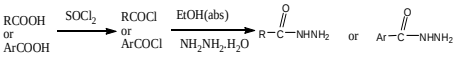
B- Materials

All chemical compounds are obtained from Fluka or Aldrich. The Naproxen is obtained from Samara, Iraq.

The reaction sequence leading to the formation of new compounds is outlined in Scheme(1).

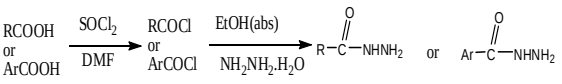
2.1 Methods

2.1.1 Preparation of hydrazide compounds (1-9) [15-17]



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 mixed of acid (5g) with (10ml) of thionyl chloride in around flask was heated to reflux during an hour and a half left to cool then added absolute ethanol (10ml) after that added hydrazine hydrate (10ml) the mixture was cooled and the solid obtained was filtered and recrystallized from ethanol .

2.1.2 Preparation of hydrazide compounds (10, 11)[18]



The hydrazides of some acids such as quinaldic acid and 3,5-dinitrobenzoic acid were prepared from mixed of acid (5g) with (10 ml) thionyl chloride in around flask and added few drops of dimethyl formamide (DMF) then the mixture was refluxed at for (1.5hr) and left to cool then added absolute ethanol (10ml) after

that added hydrazine hydrate (10ml) the mixture was cooled and the solid obtained was filtered and recrystallized from ethanol .

2.1.3 Synthesis of Oxadiazole Compounds (12-22)

A mixture of each hydrazide derivative (0.002 mole),Naproxen (0.002 mole, 0.5 gm) except terepthalic acid and glutaric acid hydrazides (0.002 mol) , Naproxen (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 dropwise (10 ml) , the mixture was neutralized by sodium hydroxid to obtaine precipitate which was filtered, dried and recrystallized from ethanol .

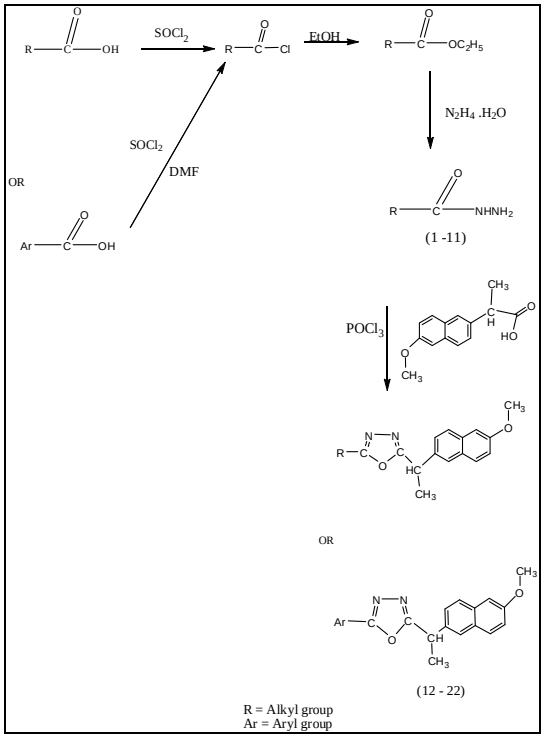


Figure 1- Scheme(1) : The Steps for Synthesis Oxadiazole Compounds of Naproxen

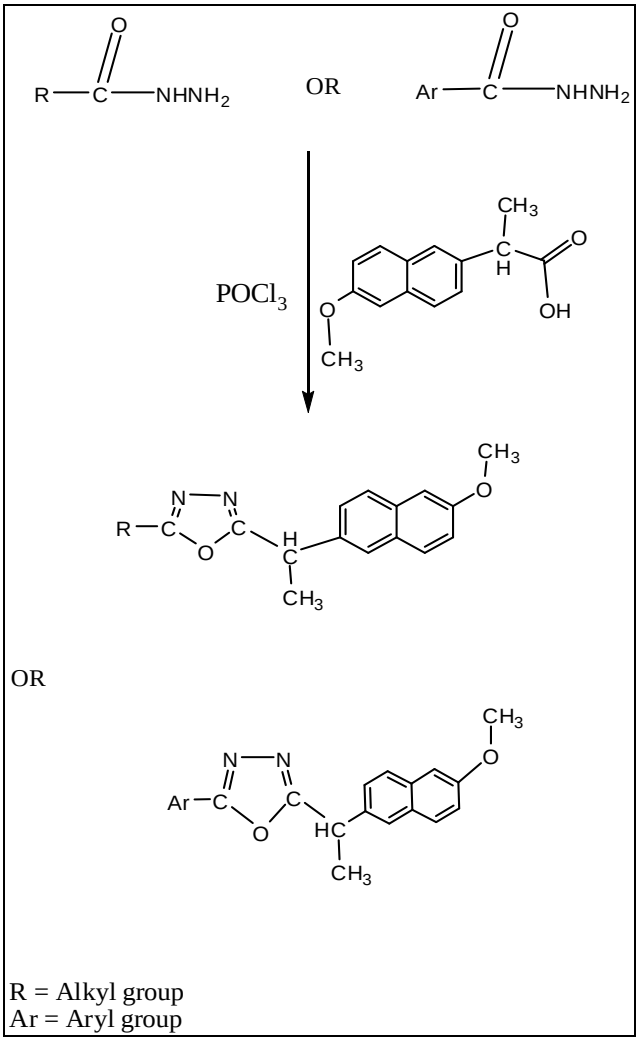
RESULTS AND DISCUSSION

The oxadiazole compounds (12-22) were synthesized from the reaction of Naproxen with hydrazide compounds of different carboxylic acids in presence of phosphorous oxychloride .

The structures of(12-22) compounds were confirmed by physical properties which are listed in Table (1) , and by spectral methods , such as FT-IR and some them by ^{1}H- NMR.

FT.TR spectra of these prepared compounds showed characteristic absorption bands at(1629 - 1642) cm^{-1},(3020- 3097) cm^{-1}, and (2837 - 2978) cm^{-}due to ν(C=N),ν(C-H) aromatic, and ν(C-H) aliphatic, . These bands and others are shown in Table(2) as shown in Figs. (2-5) .

The H-NMR spectra of compounds (14 , 15 , 20, and 21) showed the following characteristics chemical shifts (DMSO as a solvent) were appeared:doublet signal at δ(1.14,1.32,1.11,and 1.08) ppm. respectively suggested the attribution to the proton of methyl group and quartet signal at δ[(1.49-1.38),(1.74-1.53),(1.43-1.50),(1.32-1.40)] ppm. suggestingS the attribution of proton of (CH) group, a singlet signal at δ (3.74, 3.81,3.86,3.77) ppm. suggested the attribution of the protons of (OCH_3) group,the multiplet signals at δ[(7.12-8.04),(7.57-7.84),(7.06-8.13),(7.0-7.79)ppm. that could be assigned to benzene ring and naphthalene protons, as shown in Figs.(6-9) .



The mechanism of this reaction[19] is shown below, Scheme (2)

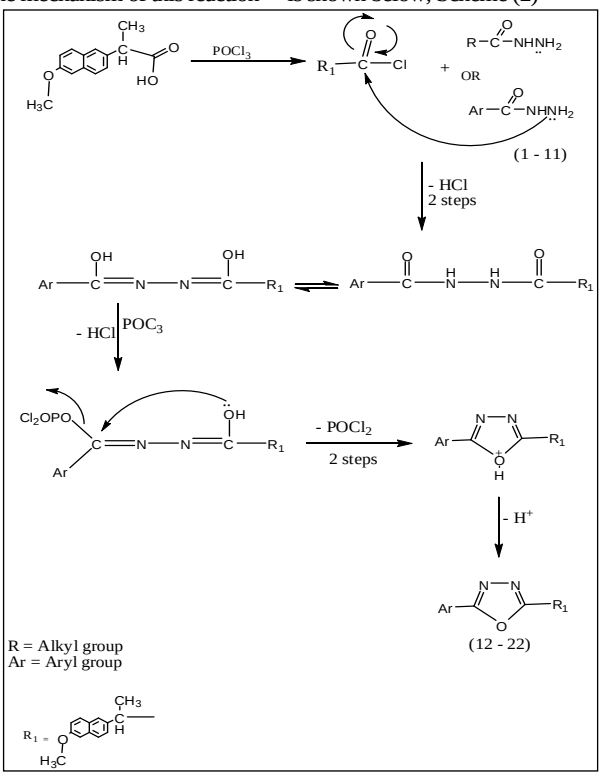
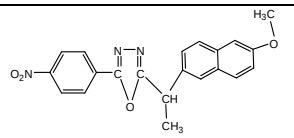
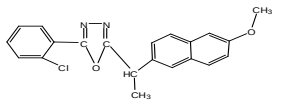
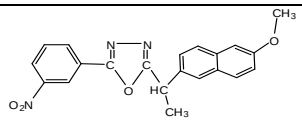
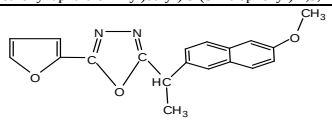
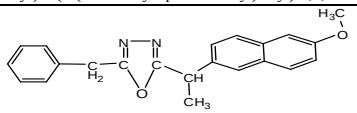
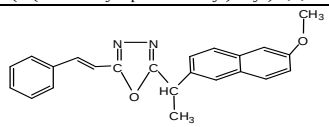
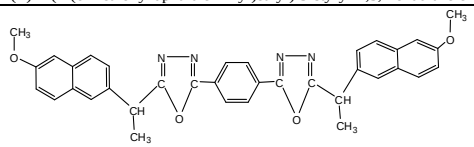
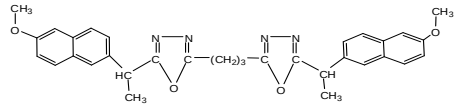
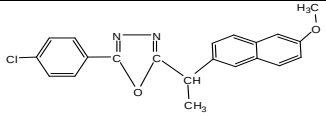
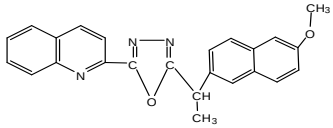
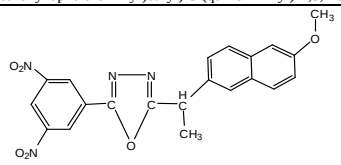


Table (1) : The Physical Properties of Oxadiazole Compounds

Comp. No.	Compound Structure	Molecular Formula	Molecular Weight	Yield %	Melting point °C	Color	R_f
12	 2-(1-(6-methoxynaphthalen-2-yl)ethyl)-5-(4-nitrophenyl)-1,3,4-oxadiazole	$C_{21}H_{17}N_3O_4$	375	70	176-178	white	0.71
13	 2-(2-chlorophenyl)-5-(1-(6-methoxynaphthalen-2-yl)ethyl)-1,3,4-oxadiazole	$C_{21}H_{17}N_2O_2Cl$	364.5	75	>250(d)	white	0.91
14	 2-(1-(6-methoxynaphthalen-2-yl)ethyl)-5-(3-nitrophenyl)-1,3,4-oxadiazole	$C_{21}H_{17}N_3O_4$	375	69	170-172	black	0.66
15	 2-(furan-2-yl)-5-(1-(6-methoxynaphthalen-2-yl)ethyl)-1,3,4-oxadiazole	$C_{19}H_{16}N_2O_3$	320	65	175-177	brown	0.87
16	 2-benzyl-5-(1-(6-methoxynaphthalen-2-yl)ethyl)-1,3,4-oxadiazole	$C_{22}H_{20}N_2O_2$	344	72	134-136	Dark green	0.59
17	 (*E*)-2-(1-(6-methoxynaphthalen-2-yl)ethyl)-5-styryl-1,3,4-oxadiazole	$C_{23}H_{20}N_2O_2$	356.16	73	179-181	orange	0.82
18	 1,4-bis(5-(1-(6-methoxynaphthalen-2-yl)ethyl)-1,3,4-oxadiazol-2-yl)benzene	$C_{32}H_{30}N_4O_4$	582.13	77	188-190	brown	0.68
19	 1,3-bis(5-(1-(6-methoxynaphthalen-2-yl)ethyl)-1,3,4-oxadiazol-2-yl)propane	$C_{33}H_{32}N_4O_4$	548.12	66	191-193	Dark brown	0.64
20	 2-(4-chlorophenyl)-5-(1-(6-methoxynaphthalen-2-yl)ethyl)-1,3,4-oxadiazole	$C_{21}H_{17}N_2O_2Cl$	364.5	70	-----	gummy	0.74
21	 2-(1-(6-methoxynaphthalen-2-yl)ethyl)-5-(quinolin-2-yl)-1,3,4-oxadiazole	$C_{24}H_{19}N_3O_2$	381.17	78	167-169	green	0. 83
22	 2-(3,5-dinitrophenyl)-5-(1-(6-methoxynaphthalen-2-yl)ethyl)-1,3,4-oxadiazole	$C_{21}H_{16}N_4O_6$	420.12	79	164 -166	Brown	0.73

Table(2) The IR characteristic bands of compounds (12-22).

Comp.NO.	ν(C=N)	ν(C- H) Ar.	ν(C-H) Aliph.	ν(C-O-C)	Other Bands
12	1604	3093	2902, 2839	1215-1261, 1029-1062	C-NO_2 856
13	1608	3076	2960, 2837	1215-1263, 1029-1060	C-Cl 813
14	1604	3059	2978, 2881	1215-1265, 1030-1072	C-NO_2 856
15	1604	3057	2937, 2837	1213-1263, 1022-1066	---------
16	1604	3068	2935, 2839	1215-1265, 1029-1076	--------
17	1604	3030	2935, 2839	1213-1263, 1028-1070	-------
18	1604	3020	2937, 2839	1213-1263, 1028-1068	-------
19	1604	3075	2939, 2839	1215-1265, 1029-1072	------
20	1602	3068	2939, 2839	1213-1267, 1029-1072	C-Cl 808
21	1604	3057	2939, 2839	1213-1263, 1022-1070	------
22	1604	3097	2980, 2939	1215-1269, 1024-1072	C-NO_2 854

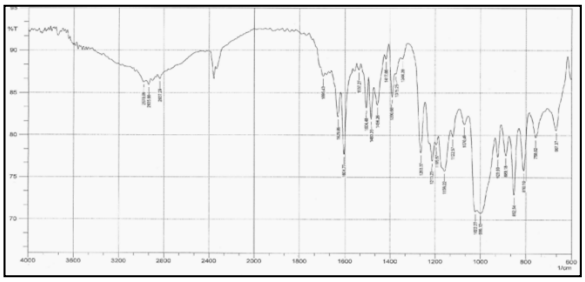


Fig.(2) FT-IR Spectrum of compound 15

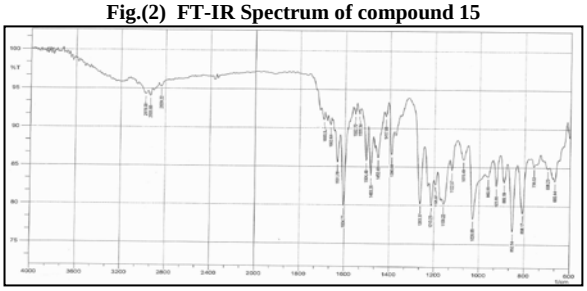


Fig.(3) FT-IR Spectrum of compound 17

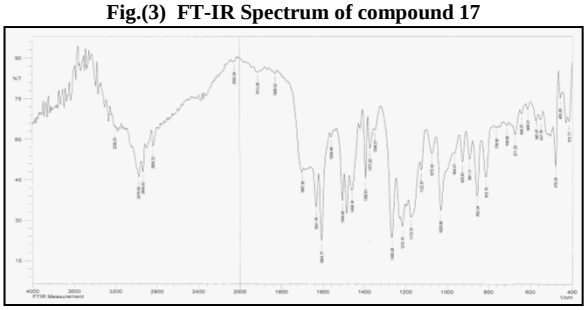


Fig.(4) FT-IR Spectrum of compound 19

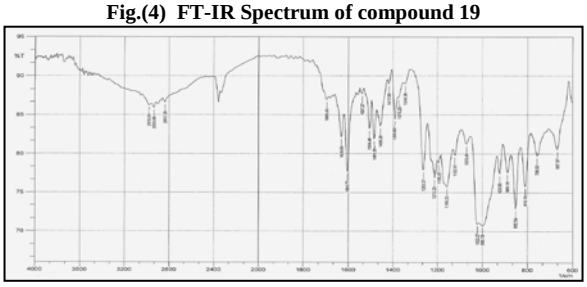


Fig.(5) FT-IR Spectrum of compound 21

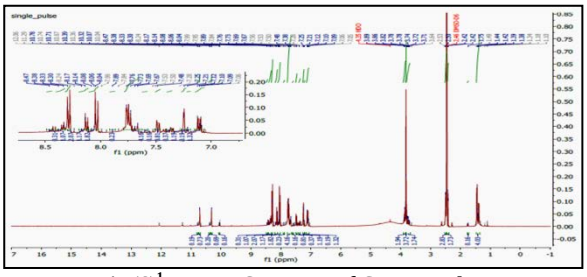


Fig.(6)^{1}H-NMR Spectrum of Compound 14

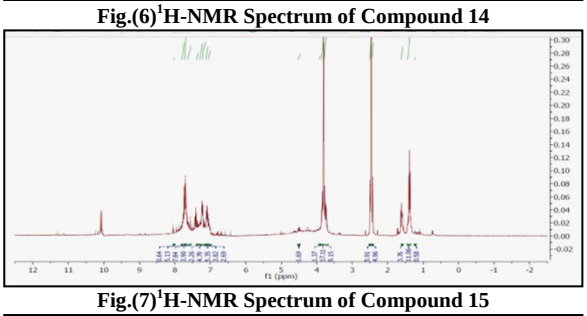


Fig.(7)^{1}H-NMR Spectrum of Compound 15

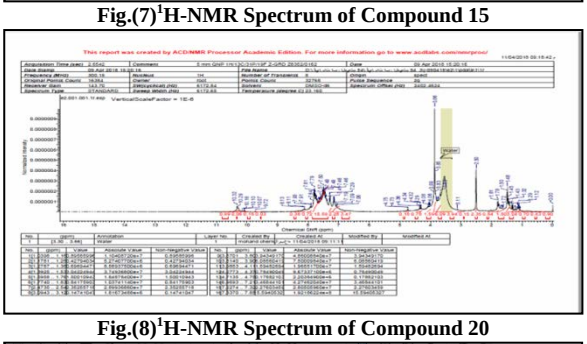


Fig.(8)^{1}H-NMR Spectrum of Compound 20

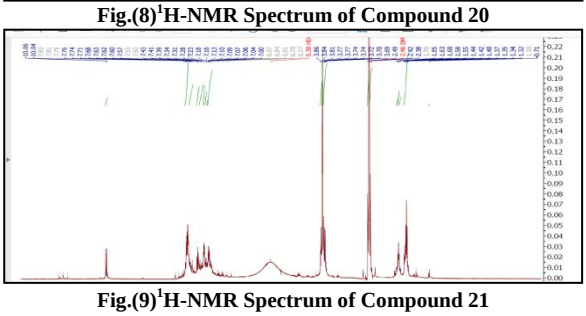


Fig.(9)^{1}H-NMR Spectrum of Compound 21

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