Synthesis and Characterization of Some New Piprazine, Phthalizines, Pyridazine, Fused1,2,4-triazole- 3 -4-b-1,3,4-oxadiazole-3- thiole and Pyrazole

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***Abstract*—** Naproxen ((S)-(+)-2-(6-methoxy-2-naphthyl) propionic acid) is a non-steroidal anti- inflammatory drug (NSAIDs) derived from propionic acid (1). A mixture of acid chloride (8g ,0.03 mole) and hydrazine hydrate (0.03mol) in (15mL) of abs. ethanol was heated to reflux during 5hrs. the mixture was cooled and the solid obtained was filtered and re crystallized from ethanol.

***Keywords*—** Piprazine, Phthalizines, Pyridazine, Fused1,2,4-triazole- 3 -4-b-1,3,4-oxadiazole-3- thiole and Pyrazole.

I. INTRODUCTION

A. Naproxen :

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) .The (S)- enantiomer is 28- fold more active than the corresponding (R)-enantiomer, (R)-isomer shows adverse side effects including renal impairment, gastrointestinal bleeding and platelet inhibition with altered haemostasis, warranting elimination of the unwanted enantiomer from the formulation (3). Heterocyclic compounds are found as construction units through several biological molecules (4), mostly are molecules which contain five and six membered ring (5). 1,3,4-Oxadiazole is the most thermally stable isomer which has attracted special attention, this is primarily due to the large number of uses in many diverse areas, including drugs, scintillation materials, dyes(6) and surface active agents (7). Pyrazole is a class of organic heterocyclic compounds containing a five membered aromatic ring structure composed of two nitrogen atoms and three carbons. But pyrazoline is a class of organic heterocyclic compounds containing a five membered not aromatic ring structure composed of two nitrogen atoms and three carbons (8).

B. Synthesis of 2-(6-methoxy naphthaline-2-yl)propane hydrazide[3] [(1)]:

A mixture of acid chloride (8g ,0.03 mole) and hydrazine hydrate (0.03mol) in (15mL) of abs. ethanol was heated to reflux during 5hrs. the mixture was cooled and the solid obtained was filtered and re crystallized from ethanol.

C. Synthesis of 2-hydrazinyl-5-(1-(6-methoxy naphthalene-2- yl)ethyl)-1,3,4-oxadiazole[4][(2)]:

A mixture of 2-(6-methoxy naphthalene-2-yl)propane hydrazide(5)(7g, 0.032mole), (15mL) of carbon disulfide, and sodium hydroxide (1.3g, 0.03mole) was dissolved in (25mL) absolute ethanol and refluxed for 7 hour or until most of the hydrogen sulfide has been evolved. Then the solvent was evaporated and the residue was dissolved in ice-water and acidified with diluted hydrochloric acid, the precipitate was filtered.The product was mixed with hydrazine hydrate and refluxed for 4hrs , then the mixture was cooled and the solid obtained was filtered and recrystallized from ethanol.

D. Synthesis of 2-(1-(6-methoxynaphthalene-2-yl)ethyl) -5-(2-(4-substitutedbenzylidene) hydrazinyl) -1,3,4-oxadiazole [6-7] [(3)]:

A mixture of compound [5] (0.005 mole, 1.5g) and 4-nitrobenzaldehyde,4-dimethylaminobenzaldehyde(0.005mol)in absolute ethanol (18 mL) and drops of glacial acetic acid was refluxed for 4 hours, the mixture was cooled and the solid was filtered then recrystallized from ethanol and collected by filtration.

E. Synthesis of 3-(5-(1-(6-methoxynaphthalene-2-yl)ethyl)-1,3,4-oxadiazol-2-yl)amino)-2-(4-substitutedphenyl)thiazolidine4-one[8-9] [(4)]:

A mixture of Schiff bases(6-7) (0.0005mol) and thioglycolic acid (0.0005 mol) was refluxed in dry benzene (15 mL) for 6 hrs . After cooling the precipitate was filtered and recrystallized from ethanol and water.

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F. Synthesis of 1-(5-(1-(6-methoxy naphthalene-2-yl)ethyl)-1,3,4-oxadiazol-2-yl)piperazine-3,6-dione[10][(5)]:

A mixture of compound [5] (0.0007 mol , 0.2g) with succinic anhydride (0.0007mol, 0.07g) dissolved in (15 ml) acetic acid and then was refluxed for 7hrs.then the mixture was poured on crushed ice. The formed solid product was filtered off and recrystallized from ethanol.

G. Synthesis of 2-(5-(1-(6-methoxynaphthalene-2-yl)ethyl)-2,3-dihydrophthalazine-1,4-dione[11][(5)]:

A mixture of compound [5] (0.0007 mol , 0.2g) with phthalic anhydride (0.0007mol, 0.1g) dissolved in (15 mL) acetic acid and the mixture was refluxed for 7hrs.then the mixture was poured on crushed ice, the formed solid product was filtered off and recrystallized from ethanol.

H. Synthesis of 2-(5-(1-(6-methoxynaphthalene-2-yl)ethyl)-1,3,4-[oxadiazol-2-yl)-7-nitro-2,3-dihydrophthalazine-1,4-dione[12] [(5)]:

A mixture of compound [5] (0.0007 mol , 0.2g) with 5-nitro phthalic anhydride (0.0007mol, 0.1g) dissolved in (15 mL) acetic acid and the mixture was refluxed for 7hrs.then the mixture was poured on crushed ice, the formed solid product was filtered off and recrystallized from ethanol.

I. Synthesis of 1-(5-(1-(6-methoxynaphthalen-2-yl)ethyl)-1,3,4-[oxadiazol-2-yl)-1,2-dihydropyridazine-3,6-dione[13][(5)]:

A mixture of compound [5] (0.0007 mol, 0.2g) with maleic anhydride (0.0007mol, 0.06g) dissolved in (15 mL) acetic acid and the mixture was refluxed for 7hrs.then the mixture was poured on crushed ice, the formed solid product was filtered off and recrystallized from ethanol.

J. Synthesis of 6-(1-(6-methoxynaphthalene-2-yl)ethyl)-[1,2,4]triazolo[3,4-b][1,3,4]oxadiazole-3-thiol[14]:

A mixture of compound [5] (0.0007 mol , 0.2g) with sodium hydroxide (0.0007mol, 0.06g) dissolved in (15 mL) carbon disulfide and (10mL)of ethanol was refluxed in water bath at 800C for 10hrs. then allowed to cool down to room temperature, poured into water, neutralized by diluted acetic acid and the solid product was filtered then re-crystallized from ethanol.

K. Synthesis of 3-amino-1-(5-(1-(6-methoxynaphthalen-2-yl)ethyl)-1,3,4-oxadiazole-2-yl)-1H-pyrazol-5(4H)-one[15]:

A mixture of compound [15] (0.0007 mol , 0.2g) with (10ml) ethyl cyanoacetate in (15 ml) ethanol was refluxed for 6hrs. ,excess solvent was distilled then filtered off and the solid was re crystallized from ethanol.

TABLE I: PHYSICAL PROPERTIES OF THE SYNTHESIZED COMPOUNDS.

Comp. No.	*Molecular Formula*	*Molecular Weight (g/mole)*	*Yield (%)*	*M.P (^oC)*	*Colour*	*Rf*
1	$C_{14}H_{14}O_3$	230	-	-	White	-
3	$C_{14}H_{16}N_2O_2$	244.29	67	194-196	Pale orange	0.89
5	$C_{15}H_{16}N_4O_2$	284.31	77	175-177	Pale yellow	0.91
6	$C_{22}H_{19}N_5O_4$	417.42	55	191-193	White	0.92
7	$C_{24}H_{25}N_5O_2$	415.20	59	193-195	Red	0.93
8	$C_{24}H_{20}N_5O_5S$	491.52	70	137-139	White	0.91
9	$C_{26}H_{27}N_5O_3S$	489.59	62	216-217	White	0.93
10	$C_{23}H_{18}N_4O_5$	430.41	77	154-155	Brawn	0.96
11	$C_{23}H_{18}N_4O_4$	414.41	78	188-190	Pale brawn	0.94
12	$C_{23}H_{17}N_5O_6$	459.41	80	228-229	Pale yellow	0.89
13	$C_{19}H_{16}N_4O_4$	364.35	82	178-179	Pale brawn	0.92
14	$C_{16}H_{14}N_4O_2S$	326.37	70	142-144	Pale green	0.89
42	$C_{18}H_{17}N_5O_3$	351.36	66	214-216	White	0.67

II. CHARACTERIZATION OF COMPOUNDS (1-15)

This part involved the synthesis of oxadiazole[32] via reaction of hydrazide derivatives[31]with NaOH in CS2,and cyclization of compound [32] with,4-nitro benzaldehyde[33] , 4-N,N-dimethyl benzaldehyde[34],.then cyclization the products with 2- mercapto acetic acid to obtain thiazolidine rings [35-36],also with succinic anhydride,phthalic anhydride,3-nitro phthalic anhydride to get phthalazin-3,8-dione [37-38-39] ,maleic anhydride to get[40],and reaction of oxadiazole[32] with NaOH/CS2 in absolute ethanol[41].and [32] with ethyl 2-cyanoacetate[15].

A. Characterization of 2-(6-methoxy naphthalene-2-yl) propane hydrazide[3]:

2-(6- methoxy naphthalene-2-yl)propane hydrazide [31] prepared by reacting of 2-(6-methoxy naphthalene -2-yl) propanoic acid with $SOCl_2$ and the product reacts with hydrazine hydrate in ethanol. The FT-IR spectrum,for hydrazide derivatives[3]shows the appearance of the characteristic absorption bands in the regions (3240,3209) cm^{-1} due to asymmetric and symmetric stretching vibration of the ($NH-NH_2$) group, the FT-IR spectrum also shows the appearance of absorption band in the region (1643) cm^{-1} due to the stretching vibration of the carbonyl group, while a new band appeared at (1589) cm^{-1}due to the stretching vibration of amide bending vibration band at (1456,1572) respectively.

B. Characterizationof2-hydrazinyl-5-(1-(6-methoxy naphthalene -2-yl)ethyl)-1,3,4-oxadiazole[5]:

The 2-hydrazinyl-5-(1-(6-methoxynaphthalene-2-yl)ethyl)-1,3,4-oxadiazole was synthesized by reaction of hydrazide derivative [3] with CS_2, KOH in absolute ethanol, hydrochloric acid and hydrazine hydrate ,added respectively. FTIR spectrum of compound [5] in figure (-) indicated the disappearance of NH_2 in the range (3176,3284) cm^{-1} and disappearance of carbonyl of amide at (1643) cm^{-1}, C-O-C asymmetric and symmetric bands appeared at(1240,1143) cm^{-1} respectively, aliphatic (CH) appeared at (2972) cm^{-1} , aromatic (CH) appeared at (3128) cm^{-1} , appearance of band at range (1593) cm^{-1} assignable to υ (C=N) of oxadiazole ring.

C. Characterization of 2-(1-(6-methoxy naphthalene-2-yl)ethyl) -5-(2-(4-nitro benzylidene)hydrazinyl)-1,3,4-oxadiazol[6],4-((2-(5-(1-(6-methoxy naphthalen-2-yl)ethyl)-1,3,4-oxadiazol-2-yl)hydrazine)methyl_-N,N-dimethyl)aniline[6,7]:

Compounds [6,7] were synthesized from the reaction of compound [5] with 4-nitrobenzaldehyde and4-dimethyl amino benzaldehyde in absolute ethanol afforded the imine. The condensation reaction of equimolar quantity of primary amine with the appropriate aromatic aldehydes is the major method to prepare series of Schiff bases. The FT-IR spectrum of compound [6] indicated the appearance of (C=N) stretching band at (1591) cm^{-1} and (C-H) aliphatic at (2918) cm^{-1} and (C-H) aromatic at (3005) cm^{-1} and (N-H) at (3080) cm^{-1} .

^{1}H-NMR spectrum of compound [34] , showed signals at δ 3.08 (6H) that could be assigned to 2(CH_3) protons, a signals at δ 3.85 (1H) that could be assigned to (NH) protons, a signal peak at δ 9.51 (1H) that could be assigned to (N=CH) proton and a multiplet signals at δ 6.72-7.63 (10 H) that could be assigned to benzene ring and naphthalene protons.

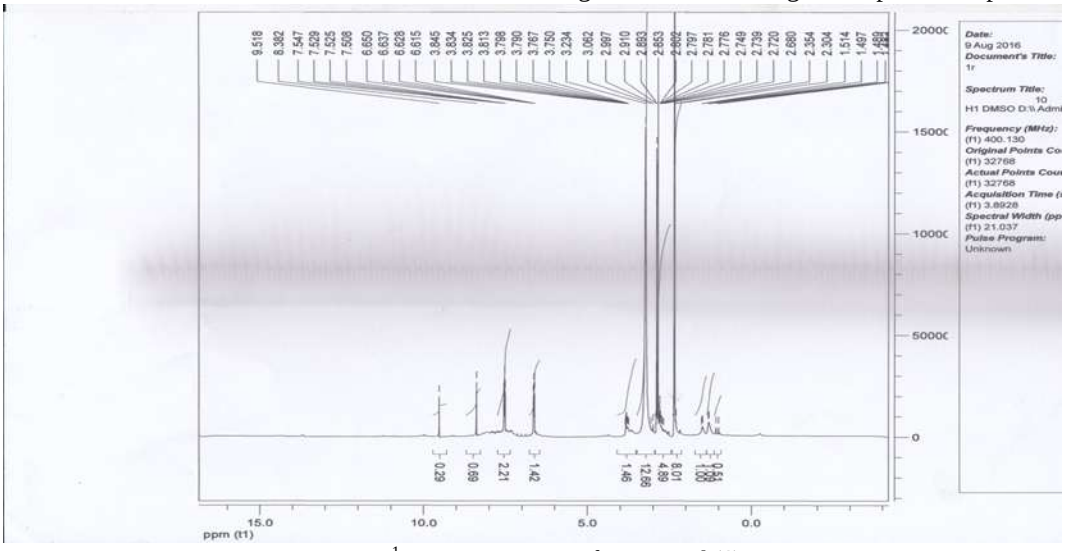

Fig. 1 ^{1}H-NMR spectrum of compound (6)

TABLE II THE IR CHARACTERISTIC BANDS OF COMPOUNDS6,7

Comp. No.	Changed part(x)	IR, KBr, υ, cm^{-1}					
		(N-H)	(C-H) Ar.	(C-H) Aliph.	(C=N)	(C=C)	Others Bands
6	*p*-C-NO_2	3112	3011	2925	1599	1478, 1530	C-NO_2 1395,1481
7	$N(CH_3)_2$	3080	3005	2918	1591	1487, 1525	N-CH_3 1228,1246

D. Characterization of compounds [8,9]:

Thiazolidine derivatives were prepared by the reaction of Schiff bases(33,34) and 2-mercaptoacetic acid in dry benzene. The FT-IR spectrum of compound [9]. Showed the appearance of carbonyl group of the thiazine in (1714) cm^{-1} and (C-H) aliphatic band at (2960) cm^{-1}, (C-H) aromatic band at (3030) cm^{-1} and (C-N) band at (1354) cm^{-1} . ^{1}H-NMR spectrum of compound [8] showed signals at δ (7.12-7.80) belong to aromatic protons, a sharp singlet at δ 3.83 ppm due to three protons of ($O-CH_3$) group,a singlet at δ 5.92 ppm (1H) that could be attributed to one proton of (S-CH) group.

TABLE III THE IR CHARACTERISTIC BANDS OF COMPOUNDS (35-36)

Comp. No	Changed part(x)	IR, KBr, υ, cm^{-1}					
		(N-H)	(C-H) Ar.	(C-H) Aliph.	(C=O)	(C-S-C)	Others Bands
8	NO_2	3109	3051	2921	1732	1097	C-NO_2 1350,1420
9	$N(CH_3)_2$	3151	3030	2960	1714	1033	N-CH3 1163

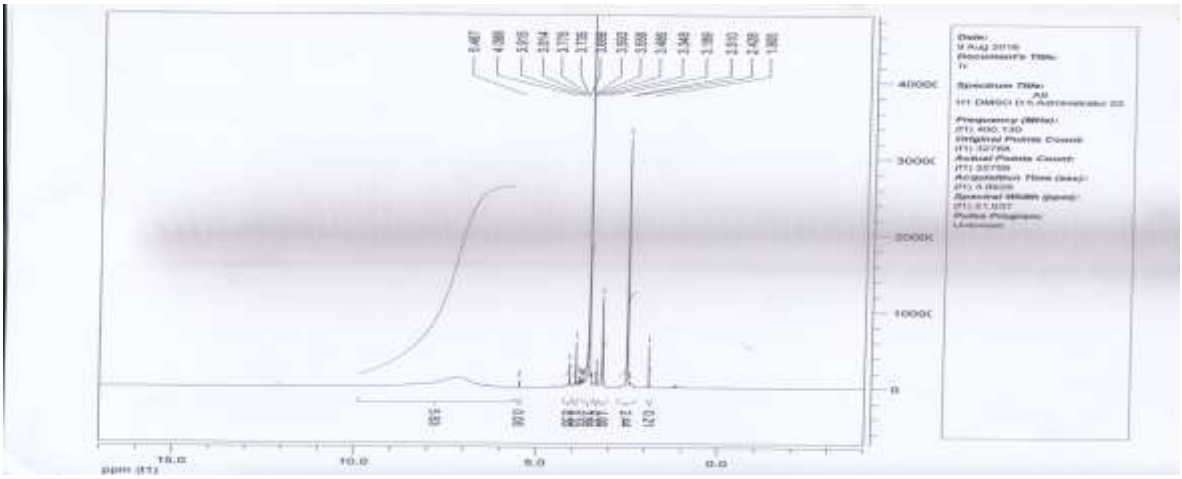

Fig. 2 ^{1}H-NMR spectrum of compound (8)

E. Characterization of componds [10-13]

Compounds [37-40] were synthesized from the reaction of compound [5] with succinic anhydride,phthalic anhydride,3-nitro phthalic anhydride and maleic anhydride respectively in the presence of acetic acid as a solvent and catalyst. The FT-IR spectrum of compound [10] indicated the appearance of N-H band at (3225) cm^{-1} and the (Ar-NO_2) substituted out of plane at (1373,1411) cm^{-1}, .The FT-IR spectrum of compound [40] in figure (3-29) shows the disappearance of the two bands of NH group in the region (3309) cm^{-1} and appearance of a band due to aromatic (C-H) group at the range (3036) cm^{-1}. carbonyl groups appeared at (1697,1647) cm^{-1}. The ^{1}H-NMR spectrum of compound [37] showed a signal at δ 8.05 ppm (1H) that could be assigned to (O=C-NH) proton , a multiplet signals at δ 6.44-7.72 ppm (1H) that could be assigned to benzene ring protons.

TABLE IV THE IR CHARACTERISTIC BANDS OF COMPOUNDS (10-13).

Comp.no	IR, KBr, υ, cm^{-1}				
	(N-H)	(C-H) Ar.	(C-H) Aliph.	(C=O)	(C=C) sy./asy
10	3225	3000	2845,2937	1722	1494,1572
11	3244	3005	2929,2987	1701	1488,1592
12	3300	3008	2934,2967	1664	1465,1591
13	3309	3036	2848,2927	1667	1498,1554

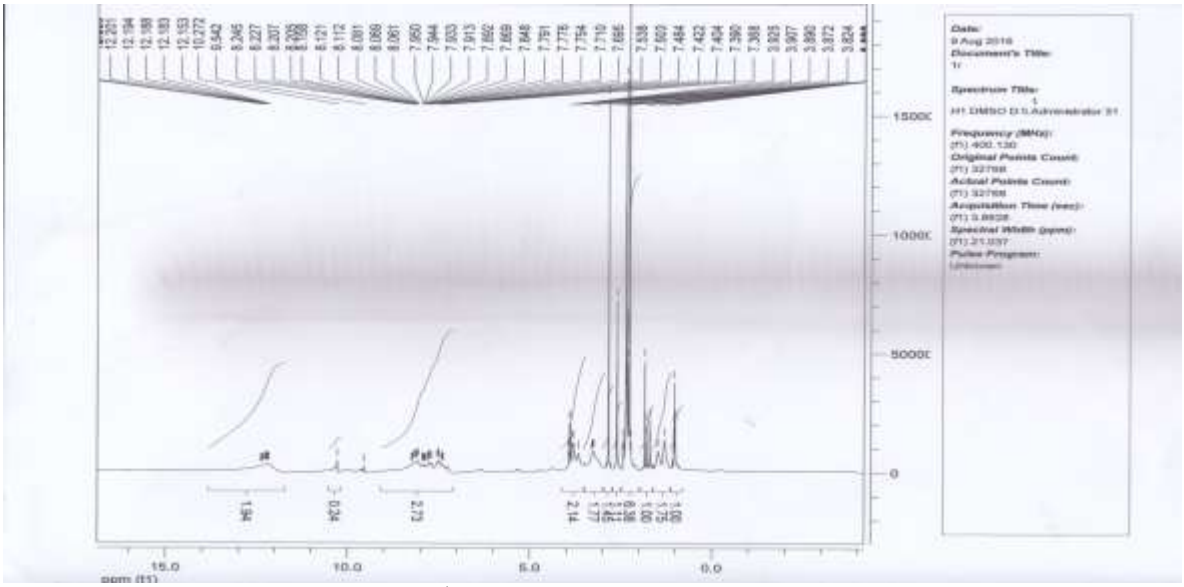

Fig. 4 ^{1}H-NMR spectrum of compound (10)

F. Characterization of6-(1-(6-methoxy naphthalene-2-yl)ethyl)-[1,3,4]triazolo[3,4-b][1,3,4]oxadiazole-3-thiol[14]:

Compound [14] was synthesized from the reaction of compound [5] with NaOH in CS_2 and in ethanol. The F.T.IR spectrum of compound [41] indicated the appearance of S-H band at (2063) cm^{-1} and C=N band appeared at (1614) cm^{-1}.

G. Characterization of 3-amino-1-(5-(1-(6-methoxy naphthalene-2-yl)ethyl)-1,3,4-oxadiazol-2-yl)1H-pyrazol-5(4H)-one[15]:

Pyrazol prepared through the reaction of oxadiazol with ethyl cyano acetate in ethanol. The FT-IR spectrum of compound [15] in figure (3-32), shows the appearance of NH_2 and NH bands in the region (3213-3255) cm^{-1}, aromatic C-H band at (3053) cm^{-1} and C=O band at (1674) $cm^{-1}$of the keto form in addition to C=N at (1646) cm^{-1}.

REFERENCES

[1] M. A. Filippa and E.I.Gasull, Experimental determination of Naproxen solubility in organic solvents and aqueous binary mixtures: Interactions and thermodynamic parameters relating to the solvation process. *Journal of Molecular Liquids*.19878-83. (2014)

[2] L. Steenkamp and D. Brady, Screening of commercial enzymes for the enantioselective hydrolysis of R, S-naproxen ester , Enzyme and microbial technology. 32, 472-477. (2003)

[3] S. D.Shinde and G. D. Yadav, Insight into microwave assisted immobilized Candida antarctica lipase B catalyzed kinetic resolution of RS-(±)-ketorolac. Process Biochemistry. (2014).

[4] E. Campaign, *J .Chemical Education*, Vol. 6, 860 (1986), 5 th Edition, *J.chem.Educ*; pp 89 (11) , 1349-1350\(2012).

[5] J.A.Joule and K. Mills "*Heterocyclic Chemistry*"5th ed Wiley, p 19(2009).

[6] K. Ladva, P. Patel, P. Upadhyay and H. Parekh, *Ind. J. Chem*. ,35B, 1062 (1966)

[7] J. A. Frump, *Chem. Rev*., 71, 483 (1971).

[8] G.A.cordell.,"*The Alkaloid Chemistry and Biology*" Vol 69 Elsevier p-1211(2010).

[9] E. M. Mohammed. Ph.D. Thesis. Baghdad University College of Science for women. (2016)

[10] S. Cao, *Journal of Fluorine Chem*., 117, 63-66 (2002).

[11] M. Noolvi, S. Agrawal, H. patel, A. Badiger, M, Gaba & A. Zambre; Arabian Journal of Chemistry ;21(50) , p;1,(2011).