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Synthesis, characterization and pharmacological activity of Ibuprofen Acyl Hydrazones and their Conversion into 1,3,4-Oxadiazoline Derivatives

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ABSTRACT

This work implicates the synthesis of Ibuprofen Acyl Hydrazones and then Converted into the new 1,3,4-Oxadiazoline derivatives that characterized by proton-NMR, FT.IR and elemental microanalysis (CHN) techniques. The intermediates and final compounds were investigated for their physicochemical properties, including the melting point, color, the yield percent, and thin-layer chromatography performed by using TLC silica gel (60) F254, Merck (Germany), to identify the purity of the products and to know the reaction endpoint. Compounds were monitored by UV light irradiation and the elution by using the following systems:: ethyl acetate: hexane (3:7), ethyl acetate, ethanol:dioxan (1:1) and methanol: chloroform (1:9). The study was performed using Swiss albino mice (25-30 g) for the pharmacological activity assessment. Hind edema template of carrageenan used for anti-inflammatory activity assessment and the analgesic activity evaluated using (writhing induced by acetic acid) and hot plate method, the results show that all the final compounds present with good anti-inflammatory plus analgesic activities exhibited in the animal model of our experimental work , we observed that the standard compound and the synthesized derivatives substantially reduced carrageenan-induced edema at all-times (2,4,6,24) hours, all chemically synthesized new compounds actually significantly reduced the number of acetic acid writhings induced in mice and finally in hot plate method there is high increase in the reaction time to painful stimulation

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INTRODUCTION

Inflammation is a portion of body tissue's complicated response to harmful stimulation (pathogens, cells damaging, or irritation) and other protection response, including blood vessels, immune cells, and finally, molecular mediators (Xie *et al.*, 1991; Kujubu and Herschman, 1992). Inflammation has the function of eliminating the initial reason of injured cells. The five classic Signs of warmth, discomfort, swelling, redness, and loss of function (Walker, 2011). Due to the wide range of pharmacological responses of acyl hydrazones such as anti-microbial, analgesic, anti-inflammatory, anti-platelet, anti-tuberculosis and anti-tumor activity (Todeschini *et al.*, 1998), N-acyl hydrazones have attracted considerable attention in medicinal chemistry, The presence of azomethine proton (HN-N=CH-) in hydrazones has attracted particular attention to the development of new drugs (Harring-

ton and Lodewijk, 1997; Mahmud *et al.*, 1996). N-Acyl hydrazone (NAH), regarded a privileged structure, was used as the basis for the design of fresh analgesic plus anti-inflammatory compounds drugs (Todeschini *et al.*, 1998), as the NAH subunit is the main pharmacophore for binding and inhibiting cyclooxygenases (COX) (Hamdy *et al.*, 2013). Several mechanisms to explain its COX recognition have been suggested. The first mechanism includes the relative acidity of the NAH moiety of amide hydrogen. The second mechanism includes the structure's (Chelucci *et al.*, 2014) capacity to stabilize free radicals in fatty acids like arachidonic acid, acyl hydrazones present with gastro-protection from the acidic moiety of NSAIDs, as well as there is evidence for cardio-protection by a significant manner (Chelucci *et al.*, 2014). A powerful structural function inherent by heterocycles that the pharmaceutical industry continues to utilize to great benefit heterocyclic compounds used for therapeutic purposes (Palit *et al.*, 2016). The five members of the oxadiazole nucleus present in heterocyclic compounds are primarily responsible for the various useful biological effects (Arora *et al.*, 2013)

Aim of work:

Synthesis of Ibuprofen acyl hydrazones derivatives that cyclized to the N-substituted1,3,4-Oxadiazolines, these compounds expected to have good analgesics and anti-inflammatory activity with lower ulcerogenic effect.

MATERIALS AND METHODS

Experimental Chemicals

1. Ibuprofen Sigma-Aldrich Germany
2. Ethanol Sigma-Aldrich Germany
3. Sulfuric acid Sigma-Aldrich Germany
4. Dichloromethane Sigma-Aldrich Germany
5. Sodium bicarbonate Sigma-Aldrich Germany
6. Hydrazine hydrate 99% CDH India
7. Benzaldehyde BDH England
8. Para nitro benzaldehyde BDH England
9. Para fluoro benzaldehyde BDH England
10. Para chloro benzaldehyde BDH England
11. Para methoxy benzaldehyde BDH England
12. Absolute Methanol Sigma-Aldrich Germany
13. Chloroform Sigma-Aldrich Germany
14. Glacial acetic acid Chem-lab NV Belgium
15. Petroleum ether BDH England
16. Anhydrous Magnesium sulfate Fluka AG Switzerland

Instruments

Electrical melting point-Stuart, FT-IR spectrophotometer SHIMADZU 8100s, 1H-NMR-Varian-Inova, C.H.N. analyzers Eager 300 for EA 1112, Chiller- Stuart, Hot plate stirrer-Stuart

Animals

Swiss albino mice of (25-30 g) weight used in our study.

Synthesis

Chemical synthesis pathway as below and shown in Figure 1 and their symbol with the chemical name listed in Table 1.

Synthesis of the compound ethyln 2-(4 isobutylphenyl) propanoate

Synthesis of ethyl ester of Ibuprofen by using Ibuprofen (0.02 mol, 4 g), which is treated in ethanol (20 ml) with the addition of the catalyst sulfuric acid about (0.5 ml). The mixture after that heated with refluxing for 8 hours, then the solution neutralized by sodium bicarbonate (100 grams per liter) to pH 8. The sample then extracted 3 times using dichloromethane and afterward dried using anhydrous magnesium sulfate. The percent of yield, physical properties and RF value present in the Table 2 (Shanbhag *et al.*, 1992)

synthesis of the compound 2-(4-isobutyl phenyl)propane hydrazide

To the ibuprofen, ethyl ester (0.02 mol) added hydrazine hydrate solution (99%) (0.1 mol) plus ethanol (30 ml) to a solution. The combination and after that heated for around 12 hours to reflux, the solution concentrated to about $\frac{1}{4}$ of the starting volume. Then the product treated with ice-cold water, Ibuprofen hydrazide, was separated under stirring as a white crystal of solids. The percent of yield, physical properties and RF values present in theTable 2 (Nakka *et al.*, 2010)

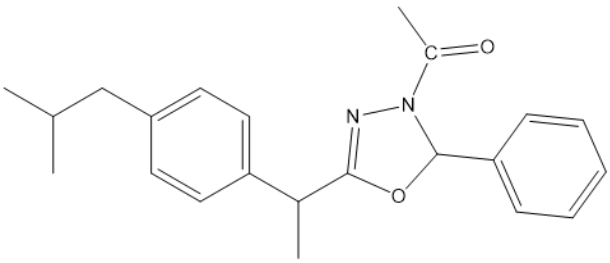
Synthesis of the compound(E)-N'-benzylidene-2-(4-isobutylphenyl) propane hydrazide and it is derivatives

By using a solution of ibuprofen hydrazide (0.0045 mol, 1g) in ethanol (30ml), aromatic aldehydes (0.0045 mol) with the addition of glacial acetic acid (3 drops, pH 4-5) (Reddy *et al.*, 2010). Its 5-hour reaction mixture has been refluxed. The

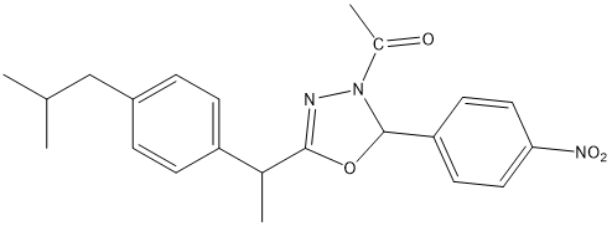
solids gained by filtration and recrystallized by ethanol forward to cooling, The percent of yield, physical properties and RF values present in the Table 2 (Gundogdu-Hizliates *et al.*, 2014).

Synthesis of the compound 1- (5-(1-(4-isobutylphenyl)ethyl)-2-phenyl-1,3,4-oxadiazol-3(2H)-yl)Ethan-1-one and it is derivatives

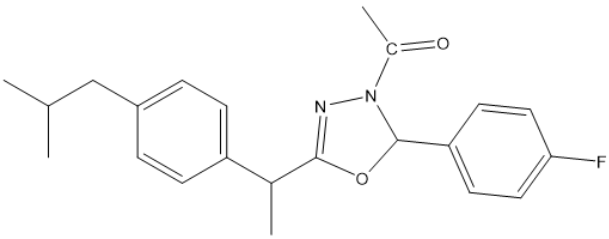
To the Ibuprofen acyl hydrazone (0.005 mol) added acetic anhydride added about (10 mL) then heated with reflux for 4 hours (Mattar, 2013) The excess acetic anhydride then evaporated. The end product obtained by using petroleum ether for purification, the insoluble impurities filtered, and the product collected after evaporation of the solvent. The single spot on TLC confirmation for the purity, The percent of yield, physical properties and RF values present in the Table 2 and the structure of the final compounds as shown in Scheme 1, Scheme 2, Scheme 3, Scheme 4, Scheme 5. (Rakesh *et al.*, 2010)



Scheme 1: The structure of OX1 compound



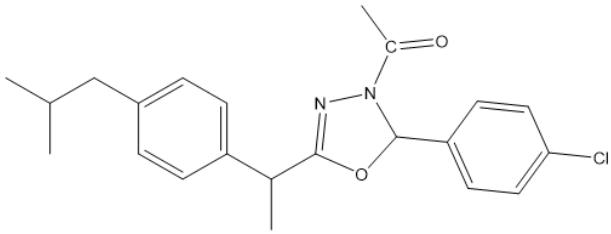
Scheme 2: The structure of OX2 compound



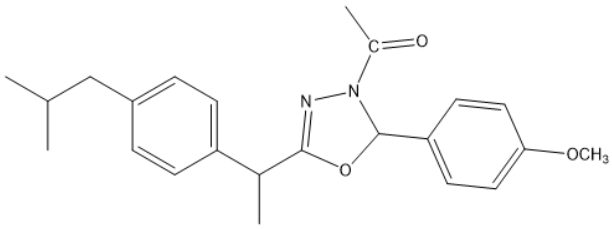
Scheme 3: The structure of OX3 compound

Anti-inflammatory model

Carrageen induced the paw edema in mice with some modification the assay in mice was



Scheme 4: The structure of OX4 compound



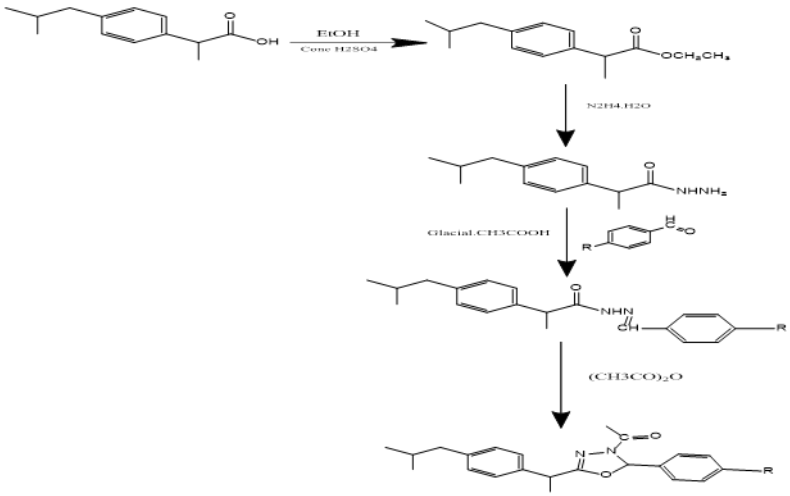
Scheme 5: The structure of the OX5 compound

achieved (Arrigoni-Blank *et al.*, 2004), the synthesized compounds and reference compound (Ibuprofen) administered through oral route by dosing 3 mg/kg soluble in 0.5 ml of sunflower oil (vehicle). The mice animals were distributed into eight groups. Each group contains six animals (n=6). All animals treated orally with oral gavage one hour once carrageenan injected, whereas the implantation of intense inflammation has been done by intradermal injection using 25 μL of both the freshly 2% w / v carrageenan remedy ready in normal saline (0.9%) throughout the right-back legs of mice. The sample teams (2–8) were subjected to carrageenan injection, whereas the treatment group (Group 1) administered a standard saline solution of 0.9 percent with 25 μL. The animals of a Group one were handled with the vehicle and operated as normal- a control group and group two carrageenan-induced the inflammation negative- control group, respectively. Group 3 mice are handled with just a standard non-steroidal anti-inflammatory drug, ibuprofen. The sample compounds (OX1, OX2, OX3, OX4, OX5) are handled to group animals (4–8), respectively. A thick of mice back feet were checked using an electronic- Vernier caliper (Numit, China) during 0,2,4,6 and 24 hrs following injection with carrageen as well as the inflammatory- edema was recorded as a percentage of variance in thickness (Δ)

Analgesic Activity

Writhing test

This experiment accomplished by acetic acid-mediated writhing assay with some modifications. Experiment compounds and Ibuprofen (standard drug) are taken orally via gastric gavage by dos-



Final compound	R
OX1	-H
OX2	-NO2
OX3	-F
OX4	-Cl
OX5	-OCH3

Figure 1: Chemical synthesis pathway of the 1,3,4-Oxadiazolinecompound derivatives

Table 1: 1,3,4-Oxadiazolinederivative chemical names and their symbol

Symbol	Name
OX1	1-(5-(1-(4-isobutylphenyl)ethyl)-2-phenyl-1,3,4-oxadiazol-3(2H)-yl)ethan-1-one
OX2	1-(5-(1-(4-isobutylphenyl)ethyl)-2-(4-nitrophenyl)-1,3,4-oxadiazol-3(2H)-yl)ethan-1-one
OX3	1-(2-(4-fluorophenyl)-5-(1-(4-isobutylphenyl)ethyl)-1,3,4-oxadiazol-3(2H)-yl)ethan-1-one
OX4	1-(2-(4-chlorophenyl)-5-(1-(4-isobutylphenyl)ethyl)-1,3,4-oxadiazol-3(2H)-yl)ethan-1-one
OX5	1-(5-(1-(4-isobutylphenyl)ethyl)-2-(4-methoxyphenyl)-1,3,4-oxadiazol-3(2H)-yl)ethan-1-one

Table 2: Physical properties of intermediates and final products

Comp	Molecular formula	Yield %	Physical appearance	M.P / C	B.P / C	Rf value	Eluent
Es	C15H22O2	91	Yellow oily liquid		262-264	0.65	Ethyl acetate: hexane (3:7)
Hz	C13H20N2O	89	White solid powder	73-74		0.83	Ethyl acetate: hexane (3:7)
S1	C20H24N2O	83	Off white powder	135-136		0.72	Ethanol: Dioxan (1:1)
S2	C20H23N3O3	76	Yellow powder	185-187		0.74	Ethanol: Dioxan (1:1)
S3	C20H23FN2O	79	Off white powder	132-133		0.66	Ethanol: Dioxan (1:1)
S4	C20H23ClN2O	77	Off white powder	133-134		0.69	Ethanol: Dioxan (1:1)
S5	C21H26N2O2	84	Off white powder	137-138		0.61	Ethanol: Dioxan (1:1)
OX1	C22H26N2O2	72	The pale yellow oily liquid		283-285	0.73	Methanol: Chloroform (1:9)
OX2	C22H25N3O4	70	The dark yellow oily liquid		291-293	0.75	Methanol: Chloroform (1:9)
OX3	C22H25FN2O2	73	The pale yellow oily liquid		284-285	0.77	Methanol: Chloroform (1:9)
OX4	C22H25ClN2O2	71	The pale yellow oily liquid		283-284	0.76	Methanol: Chloroform (1:9)
OX5	C23H28N2O3	74	The pale yellow oily liquid		290-291	0.69	Methanol: Chloroform (1:9)

ing of 3 mg/kg soluble in 0.5 ml of sunflower oil (vehicle). The number of writhings detected in each mouse was calculated over 15 minutes (five minutes that after acetic acid was given). (Raghdah *et al.*, 2019) To measure the efficacy of analgesia, the inhibition percentage (I %) for the numbers of writhings (abdominal-restrictions) were obtained and calculated as the following formula:

Inhibition %(I%) = (Nc –Nt /Nc)×100

Nc = average of writhing numbers in the negative control group, Nt = average of writhing numbers in the treated groups.

Hot plate test

The hot plate procedure in mice has been one of the essential methods of evaluating analgesic behavior. In 0.5ml of sunflower oil (vehicle) solution, the test compounds and ibuprofen (standard drug) are taken orally at a dosage of 3 mg/kg. After one hour among all oral procedures, animals have been placed on the hot plate inside a glass cylinder that was well controlled and preserved at 55±1C. A reaction time, its time differential between placing the animals on both the hot plate ground and the occurrence of jumping or leakage with fore-hind paws is checked. It was taken into consideration that now the cut-off time should not reach 20 seconds to prevent the paws from harming.

Statistical analysis

In this research, data from all experimental studies mentioned as mean± standard deviation(S.D.). Data analysis (ANOVA) is carried through by the Dennett test. Probability values ($P<0.05$) were regarded as statistically significant

RESULTS AND DISCUSSION

The FT-IR spectrum of the oxadiazoline compound derivatives

The IR-spectra for the synthesized compounds achieved through the KBr-disc procedure using FT.IR.8400S.SHIMADZU, in the Lab of Pharmaceutical-Chemistry Department/pharmacy college /Basrah- University, all the compounds show disappearance of the N-H band of the acyl hydrazone derivatives as well as shifting in the

Table 3: Elemental analysis of the final compounds

Com-pound	Molecular weight	Molecular formula	Ele-ment	Calculated elemental analysis%	Observed Elemental analysis%
OX1	350.46	C22H26N2O2	C	75.40	74.92
			H	7.48	7.37
			N	7.99	8.15
OX2	395.46	C22H25N3O4	C	66.82	67.26
			H	6.37	6.49
			N	10.63	10.35
OX3	368.45	C22H25FN2O2	C	71.72	72.19
			H	6.84	6.99
			N	7.60	7.38
OX4	384.9	C22H25ClN2O2	C	68.65	69.05
			H	6.55	6.27
			N	7.28	7.43
OX5	380.49	C23H28N2O3	C	72.60	73.09
			H	7.42	7.51
			N	7.36	7.47

Table 4: Effect of Ibuprofenand the newly prepared compounds (3 mg/kg) on carrageenan that inducedinflammation of mice hind paw's.

Group	Thickness -variation Δ (mm) in paw edema (% Inhibition)			
	2 h	4 h	6 h	24 h
Normal-control	0.48±0.48	0.31±0.52	0.23±0.29	0.16±0.19
Negative-control	2.46±0.55	2.92±0.57	3.21±0.62	1.92±0.86
Positive-control (Ibuprofen)	0.41±0.42*** (83%)	0.44±0.28*** (85%)	0.34±0.52*** (89%)	0.42±0.96*** (78%)
OX1	1.32±0.49** (46%)	1.35±0.32*** (53%)	1.27±0.39*** (60%)	0.82±1.15** (57%)
OX2	1.15±0.38*** (53%)	1.1±0.47*** (62%)	1.05±0.91*** (67%)	0.79±0.81*** (59%)
OX3	1.18±0.69*** (52%)	1.12±0.62*** (61%)	1.16±0.88*** (64%)	0.85±0.79*** (55%)
OX4	1.08±0.84*** (56%)	1.13±0.65*** (61%)	1.11±0.44*** (65%)	0.79±0.91*** (59%)
OX5	1.17±0.89*** (52%)	1.09±0.17*** (62%)	1.1±0.34*** (65%)	0.81±0.67*** (69%)

Each value is the mean± S.D. for 6 mice, *p<0.05,**p<0.01, ***p<0.001 compared with normal- control. Data analyzed throughone way ANOVA then by Dennett's-test.

C=O band to more than 1700 cm^{-1}, this indication for the formation of the 1,3,4-oxadiazoline derivative (Silverstein *et al.*, 2005)

The FT-IR spectrum of OX1

The compound(OX1) displays a moderate absorption band at 3012 cm-1 referring to aromatic C-H stretching, C-H stretching linked to high-medium bands 2958-2931 cm-1, solid band at 1708 cm-1 referring to C=O stretching, Medium band at 1608 cm-1 assigned to C=N stretching, heavy bands assigned to aromatic C=C in 1527 cm-1, 1458 cm-1, and 1419 cm-1.

The FT-IR spectrum of OX2

The compound(OX2) displays a moderate absorption band at 3062 cm-1 referring to aromatic C-H stretching, high-medium bands assigned C-H stretching of both the aliphatic alkyl group at 2958-2870 cm-1, solid band at 1712 cm-1 referring to C=O

Table 5: Anti-nociception effect of Ibuprofen and newly prepared compounds (3 mg/kg) by the acetic acid that inducing mice writhing's.

Group	Number of writhings	Inhibition (%)
Negative control (vehicle)	44.25 ± 6.18	-
Positive control (Ibuprofen)	13.28 ± 2.42 ***	69.98
OX1	26.57 ± 6.54 **	39.95
OX2	21.85 ± 5.37 ***	50.62
OX3	22.36 ± 5.91 ***	49.46
OX4	19.98 ± 3.81 ***	54.84
OX5	20.57 ± 5.24 ***	53.51

Each value is the mean ± S.D. for 6 mice, *p<0.05,**p<0.01, ***p<0.001 compared with normal-control. Data analyzed using one way ANOVA then by Dennett's-test.

Table 6: Anti-nociception effect of Ibuprofenand the newly prepared compounds (3 mg/kg) through the hot-plate procedure in mice.

Group	Reaction time (seconds)	Inhibition (%)
Negative control (vehicle)	3.45 ± 2.25	-
Positive control (Ibuprofen)	11.58 ± 2.21 ***	70.20
OX1	6.52 ± 1.74 **	47.08
OX2	7.41 ± 1.85 ***	53.44
OX3	6.95 ± 2.31 ***	50.35
OX4	7.12 ± 1.84 ***	51.54
OX5	6.15 ± 2.35 **	43.90

Each value is the mean ± S.D. for 6 mice, *p<0.05,**p<0.01, ***p<0.001 compared with normal -control. Data analyzed through one way ANOVA then by Dennett's-test

stretching, moderate band at 1608 cm-1 referred to C = N stretching, powerful bands at 1527 cm-1, 1458 cm-1 and 1419 cm-1 assigned to aromatic C = C stretching

The FT-IR spectrum of OX3

The compound(OX3) shows a moderate absorption band at 3020 cm-1 referring to aromatic C-H stretching, a powerful medium band related to C-H stretching of the aliphatic alkyl group at 2955-2870 cm-1, a powerful band at 1728 cm-1 referring to C=O stretching, a moderate band at 1608 cm-1 related to C = N stretching, a powerful band at 1512 cm-1, 1458 cm-1 and 1423 cm-1 assigned to the aromatic C=C

The FT-IR spectrum of OX4

The compound(OX4) shows a moderate absorption band at 3012 cm-1 referring to aromatic C-H stretching, strong-medium bands relating to C-H stretching of the aliphatic alkyl group at 2958-2870 cm-1, powerful band at 17024 cm-1 referring to C=O stretching, powerful band at 1600 cm-1 related to C=N stretching, powerful bands at 1508 cm-1, 1462 cm-1 and 1427 cm-1 assigned to aromatic C=C stretching

The FT-IR spectrum of OX5

The compound(OX5) displays a moderate absorption band at 3024 cm-1 referring to aromatic C-H stretching, a high-medium band belonging to C-H stretching of the aliphatic alkyl group at 2954-2931 cm-1, a solid band at 1701 cm-1 referring to C=O stretching, a moderate band at 1604 cm-1 linked to C=N stretching, a powerful band at 1512 cm-1, 1465 cm-1 and 1419 cm-1 assigned to aromatic C=C

1H.NMR Spectrum of the oxadiazoline compounds derivatives

1H.The NMR spectrum of synthetic OX derivatives used in solutions for dimethyl sulfoxide. All of the above spectra had a peak of 2,5 ppm due to DMSO solvent (Field *et al.*, 2001)

1 H.NMR Spectrum of OX1 compound

The compound OX1 showed aliphatic signals at 0.85 ppm as a doublet linked to six protons of both the two methyl groups at the isobutyl moiety, doublet signal at 1.32 ppm linked to the ethyl moiety protons (CH3),there is nonet signal present at 1.81 ppm related to the proton (-CH-) of the isobutyl moiety ,also there is singlet-signal at 2.11 ppm linked to the

(CH3) protons of the acetyl group adjacent to oxadiazoline ring, there is another doublet signal at 2.50 ppm linked to the (-CH2-) protons of the isobutyl group, quartet signal at 3.75 ppm belong to the (-CH-) proton of the ethyl group, singlet-signal at about 6.91 ppm linked to the (-CH-) proton of the oxadiazole ring,while the multiplet between 7.33- 7.91 ppm linked to the aromatic (=CH-) protons

1 H-NMR Spectrum of OX2 compound

The compound OX2 showed aliphatic signals at 0.86 ppm as doublet linked to six protons of the two methyl group related to the isobutyl moiety, doublet signal at about 1.34 ppm linked to the (CH3) protons of the ethyl moiety, there is nonet signal present at 1.82 ppm related to the proton (-CH-) of the isobutyl moiety,also there is singlet signal at 2.15 ppm linked to the (CH3) protons of the acetyl group adjacent to oxadiazoline ring, there is another doublet signal at about 2.52 ppm linked to the (-CH2-) protons of the isobutyl group, quartet signal at 3.77 ppm belong to the proton (-CH-) of the ethyl group, singlet-signal at 7.11 ppm related to the proton (-CH-) related to the oxadiazole ring, while the multiplet between 7.24-8.51 ppm linked to the aromatic (=CH-) protons

1 H.NMR Spectrum of OX3 compound

The compound OX3 showed aliphatic signals at 0.87 ppm as doublet linked to six protons of the two methyl group of the isobutyl moiety, doublet signal at 1.33 ppm linked to the (CH3) protons of the ethyl moiety,there is nonet signal present at 1.81 ppm related to the proton (-CH-) of the isobutyl moiety ,also there is singlet signal at 2.13 ppm linked to the (CH3) protons of the acetyl group adjacent to oxadiazoline ring, there is another doublet signal at about 2.54 ppm related to the (-CH2-) protons of the isobutyl group, quartet signal at about 3.79 ppm belong to the (-CH-) proton of the ethyl group, singlet- signal at 7.07 ppm related to the proton (-CH-) of the oxadiazole ring,while the multiplet between 7.40-8.35 ppm linked to the aromatic (=CH-) protons

1 H.NMR Spectrum of OX4 compound

The compound OX4 showed aliphatic signals at 0.84 ppm as doublet related to six protons of the two methyl group linked to the isobutyl moiety, doublet signal at 1.36 ppm related to the protons (CH3) of the ethyl moiety ,there is nonet signal present at 1.79 ppm related to proton (-CH-) of the isobutyl moiety ,also there is singlet signal at 2.17 ppm linked to the (CH3) protons of the acetyl group adjacent to oxadiazoline ring, there is another doublet signal at about 2.53 ppm related to the (-CH2-) protons of the isobutyl group , quartet signal at about 3.81 ppm belong to the proton (-CH-) of the ethyl group, singlet-signal at 6.84 ppm related to the (-CH-) proton of the oxadiazole ring, while the multiplet between 7.33-8.20 ppm related to the aromatic (=CH-) protons

1 H.NMR Spectrum of OX5 compound

The compound OX5 showed aliphatic signals at 0.83 ppm as doublet linked to six protons of the two methyl group related to the isobutyl moiety, doublet signal at 1.33 ppm related to the protons (CH3) of the ethyl moiety, there is nonet signal present at 1.75 ppm related to the proton (-CH-) of the isobutyl moiety, also there is singlet- signal at 2.15 ppm linked to the (CH3) protons of the acetyl group adjacent to oxadiazoline ring, there is another doublet signal at about 2.52 ppm related to the (-CH2-) protons of the isobutyl group, quartet signal at 3.84 ppm belong to the (-CH-) proton of the ethyl group, singlet-signal at 4.02 ppm linked to the (-O-CH3) protons group,also there is singlet -signal at 6.94 ppm linked to the (-CH-) proton of the oxadiazole ring, while the multiplet between 6.76- 7.93 ppm linked to the aromatic (=CH-) protons

C.H.N. Analysis

The elemental analysis of prepared compounds show that the measured value in a good agreement with the calculated values as shown in Table 3

Biological activity

Anti-inflammatory effects

Analgesic effects

Carrageen-inducing, the mice, paw edemas was a known inflammatory template for evaluating compounds anti-inflammatory activity in our analysis, we observed that the standard compound and the synthesized derivatives substantially reduced carrageenan-induced edema at all-times (2,4,6,24) hours, by inhibiting the cyclooxygenase enzyme that is responsible for prostaglandin synthesis, all the compounds appear with good inhibition between (60% - 67%) after 6 hours as shown in Table 4. By testing their efficacy centrally or peripherally, the anti-nociception activity of the newly synthesized compounds can be checked; The core analgesia was properly evaluated just using a hot plate sample, even while the peripheral analgesia was assessed using acetic acid to cause writhing. (writhing test). The results can be observed in Table 5 proved that the standard drug Ibuprofen and all chemically synthesized new compounds actually significantly reduced the number of acetic acid writhings induced in mice going to be starting with the parent drug (Ibuprofen) that give (69.98%) and the derivatives OX4 and OX5 give more potent analgesic activity,

(54.48 %, 53.51 %) respectively. In the reaction-time of pain various responses to hot plate trial through thermal stimulation which can be shown inTable 6, the positive control Ibuprofen (3mg/kg) with marked increase in the reaction-times from about 3.45 s at negative- control group to 11.58 s, also there is significant increase in the reaction time of the all synthesized compounds.

CONCLUSIONS

The study included the synthesis of the new compounds of 1,3,4- Oxadiazoline derived from Ibuprofen acyl hydrazones; the synthesized compounds have promising anti-inflammatory and analgesic activity

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