RESEARCH ARTICLE

Synthesis, Characterization and Preliminary Antimicrobial and Anti-inflammatory Evaluation of New Ibuprofen Hydrazide Derivatives

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Received: 12th December, 2022; Revised: 10th January, 2023; Accepted: 25th February, 2023; Available Online: 25th March, 2023

ABSTRACT

Non-steroidal anti-inflammatory medicines (NSAIDs) are medicines that are distributed widely across the world due to their ability to reduce pain and inflammation. In order to boost the drug's efficacy and reduce its harmful side effect like GIT ulcers and bleeding, a newly synthesized series of 5-(1-(4-isobutylphenyl) ethyl)-1,3,4-oxadiazole-2-thiol derivatives compounds (C, C 1-3) were prepared from the reaction of ibuprofen hydrazide with carbon disulfide followed by reaction with various Aryl/alkyl halide. All target compounds were tested for antimicrobial efficacy against various strains of bacteria (G+ve, S. *pyrogenes* and *S. aureus*) and (G-ve, *E. coli* and *Klebsiella pneumoniae*). Additionally, fungus species (*Candida albicans*). Compound C showed good antimicrobial activity for both bacterial strains. At the same time, Compound C1 have the best ant-bacterial activity compared with other synthesized compounds for both (G+ve), and (G-ve) bacteria, and compound C3 was the most affected one as antifungal. The compound C2 was with lowest antimicrobial activity. All of the produced compounds were examined for their anti-inflammatory activity using (egg-white generate edema) and the compounds (C, C1, C3) showed good efficacy when compared to ibuprofen (stander) FTIR and ^{1}H-NMR spectroscopy were used to analyze all of the final products.

Keywords: Anti-inflammatory activity, Antimicrobial, Carbon disulfide, Ibuprofen.

International Journal of Drug Delivery Technology (2023); DOI: 10.25258/ijddt.13.1.61

How to cite this article: Kamms ZD, Hadi MK. Synthesis, Characterization and Preliminary Antimicrobial and Anti-inflammatory Evaluation of New Ibuprofen Hydrazide Derivatives. International Journal of Drug Delivery Technology. 2023;13(1):376-381.

Source of support: Nil.

Conflict of interest: None

INTRODUCTION

Inflammation is the body response to adverse stimuli like toxic chemicals, damaged cells, infections, or irradiation. It acts by removing harmful stimuli and allowing tissue recovery to begin. Inflammation can result in many chronic ailments such as cardiovascular and intestinal problems, diabetes, arthritis, and cancer. And it's characterized by aches, flushing, swelling, warmness and destruction in tissue function. Each one was brought on by localized immune, vascular, and inflammatory cell reactions to infection or injury.[1] Inflammation is caused by activated cellular components as well as the presence of biochemical mediators such as[1] cytokines (interleukin-1), kinases, and transcription, in addition to arachidonic acid metabolites (prostaglandins PGs), which have a part in the pathogenesis of inflammatory diseases such asthma, arthritis, and cancer.[1] Because of their capacity to reduce inflammation and their analgesic effect, non-steroidal anti-inflammatory medicines (NSAIDs) are extensively employed across the world.[2] The anti-inflammatory activity of NSAIDs resulted from their ability to prevent the synthesis of prostaglandin production from arachidonic acid by inhibiting the [1]enzymes cyclo-oxygenase-1 (COX-1[1]) and cyclo-oxygenase-2[1] (COX-2[1]).[3,4] Long-term use of NSAIDs can cause a variety of significant adverse effects, including GIT bleeding. As a result, several studies have been conducted to reduce these side effects and increase their anti-inflammatory impact.[5] Oxadiazoles are heterocyclic compounds with a five-membered ring structure that contains two nitrogens' and one oxygen atom.[6] There are four main classes of oxyadiazoles, but the most active and effective is 1,3,4-oxadiazole, which contains a huge number of physiologically active molecules from several pharmacological classes. So many 1,3,4 oxadiazole compounds with increased biological and pharmacological activities, such as antimicrobial, anti-inflammatory, and anticancer properties, have been developed.[7] This project aims to create a novel powerful NSAID agent derived from ibuprofen by derivatizing the carboxylic group of NSAIDs with a heterocyclic system and then testing their antimicrobial, and anti-inflammatory activity.[5]

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EXPERIMENTAL SECTION

Chemistry

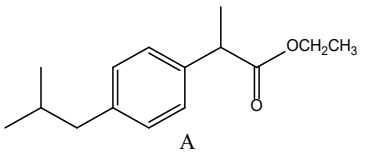
Organic solvents, hydrazine hydrate, carbon disulfide, 4-methoxyphenacylbromide, 4-hydroxyphenacylbromide, and methyl iodide were all given by the Sigma Aldrich Company for use in the synthesis. In contrast, the State Company for Drug Industries was robbed of its ibuprofen supply (SDI, Samara, Iraq). Without additional purification, all chemicals and reagents were used. The melting points of every target chemical synthesized were assessed using (Stuart SMP30 Apparatus). They were all adamant (uncorrected), or "thin-layer chromatography (TLC)," was used with aluminum-precoated silica gel sheets to follow every stage of the synthesis (Germany, Merck). University of Baghdad-College of Pharmacy provided a UV 254 nm lamp to check the spots on the intermediate and finished produced compounds. The measuring unit (cm^{-1}) was used with the FTIR (Shimadzu, Japan).

Preparation of Ibuprofen ethyl ester [2-(4- Isobutyl phenyl) Propanote] Compound A[8]

Ibuprofen, (0.028 moles, 6 mg) was dissolved in 100% ethanol and agitated while (0.5 mL) H_2SO_4 was added drop by drop over the course of 10 minutes. The mixture was then reacted for eight hours at 77°C using TLC to validate the reaction. Finally, the mixture was put into a beaker containing crushed ice and neutralized with $NAHCO_3$ (10% w/v). Yellowish oil was obtained *via* separation with ethylacetate, Yield: 85%, R*f* = 0.71 (ethylacetate, n-hexane 3:4), IR (v cm^{-1}): (c=o) str. ester is 1731, (c-o) stre. ether is (1160), (C-H) asymm. stretch. of CH_3, CH_2 (2953), (C-H) Symme. stretch. of CH_3, CH_2 is (2870) (Figure 1A).

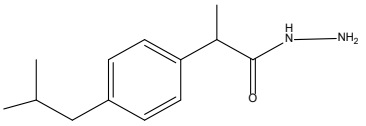
Synthesis of Ibuprofen hydrazide [2-(4-lsobutylphenyl) propane hydrazide] Compound B [9]

Compound **A** (0.013 mole, 3 gm) was mixed with (3 mL, 0.064 mole) hydrazine hydrate 100% in 25 mL of absolute ethanol, which then reflexed for 22 hours in 78ºC and TLC monitored it. The resultant solution was set aside until it cooled after the reflex time was completed. Then removed the excess solvent, ice was added, and the end product was achieved by filtrations, washing numerous times with D.w. Drying and recrystallization from ethanol. White powder, Yield 93%, MP (75-78ºC), R*f* = 0,48 (Chlorophorm: ethyl acetate 7:3), IR (v cm^{-1}): 1684 (C=O) str. of amide, 3270, 3208 (N-H) str. of hydrazide, 3025: (C-H) str. of aromatic ring, 2955, 2917: (C-H) asymm.str. of CH_3, CH_2, 2872, 2847: (C-H) symm.str of CH_3, CH_2 (Figure 1B).



A

Figure 1A: Preparation of Ibuprofen ethyl ester Compound A.



B

Figure 1B: Synthesis of Ibuprofen hydrazide Compound B.

Synthesis of 5-(1-(4-isobutylphenyl) ethyl)-1,3,4-oxadiazole-2-thiol Compound C[10]

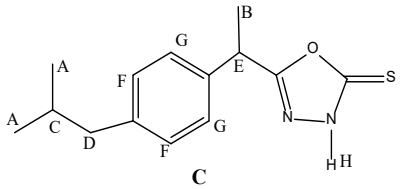
The compound B (1.30 gm, 0.006 mole) in 50% of absolute ethanol-water solvent mixture (30 mL), (2.2 gm, 0.03 mole) of CS_2 was added drop by drop with continuous stirring for 5 to 10 minutes, then KOH was added gradually (0.006 mole, 0.33 gm). After the mixture was reflexed for (17 hours), the reaction continued until the vaporization of all of CS_2 gas (the reaction was monitored by lead acetate paper and TLC). When the reflex time ended, the mixture was poured into the beaker containing 25 mL of crushed ice, then concentrated HCL was used to neutralize the mixture to PH of 2–3. The formed precipitate was filtered, dried and purified by (acid-base conversion method). White powder, yield 82%, MP (94ºC), R*f* = 0.77 (Chlorophorm: ethyl acetate 5.5:2.5), IR (v cm^{-1}): 3120: (N-H) str. of thioamide of oxadiazole ring, 3079, 3028 (C-H) str. of Ar-H, 2955, 2932: (C-H) str. of asymm.CH_3.CH_2,2908,2866: (C-H) str. of symm.CH_3.CH_2, 1612:(C=N) stre. of oxadiazole ring,1516, 1462:(C=C) of Ar ring,1273:(C=S) stre of oxadiazole,1176:(C-O-C) str. of cyclic ether of the ring. ^{1}H-NMR: 0.871 (6H, d, CH_3 (A)), 1.61(^{1}3H, d, CH_3 (B)); 1.81 (1H, m -CH (C)); 2.41 (2H, d-CH_2 (D)), 4.16 (1H, q-CH (E)) ,7.04-7.18 (4H, m-CH of Ar. (F, G)),13.28 (1H, s-SH of oxadiazole(H)) (Figure 1C).

Synthesis of S-alkylated Derivatives of 15-(1-(4-isobutylphenyl) ethyl)-1,3,4-oxadiazole-2-thiol derivatives Compound C (1-2)[11]

Solution of compound **C** (0.002 mole, 0.5 gm) and (0.002 mole, 0.07 gm) of NaoH in absolute ethanol was stirred for 5 minutes, then mixed with different alkyl/aryl halide (1-2) (0.002 mole) which were added separately, stirring for 5 minutes for (C2) and reflex for 30 minutes for (C1). The mixture was carefully observed by TLC. For compound (C1) the solid precipitate was obtained by filtration and recrystallized from ethanol. For (C2) pale yellowish oil was obtained by separation with Chlorophorm (Figure 2A).

Synthesis of S-alkylated derivatives of 15-(1-(4-isobutylphenyl) ethyl)-1,3,4-oxadiazole-2-thiol 1derivatives compound C3[12]

Compound 5 (0.5 gm, 0.002 mole) was dissolved in 8-10 mL of D.W, in the presence of 0.002 mole, 0.2 mL of Triethylamine with



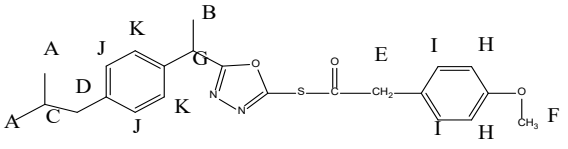
C

Figure 1C: Synthesis of Compound C.

stirring for 5 minutes or to dissolved completely, then (0.002 mole, 0.6 gm) of 4-bromophenacylbromide dissolving in 1-mL of DMF was added drop by drop to the mixture and left overnight with continuous stirring. The solid product was gained by filtration and washing with cold D.W several time S-(5-(1-(4-isobutylphenyl) ethyl)-1,3,4-oxadiazol-2-yl)2-(methoxyphenyl) ethanethioate (C1): white powder, yield 60%, MP= (67), R*f* = 0.6 (Chlorophorm: ethylacetate 5.5:2.5), IR (vcm^{-1}):3055:(C-H) stret. of Aromatic, 2954,2916:(C-H) asymm. Str. of CH_2, CH_3,2870, 2843:(C-H) symm. Str. of CH_2, CH_3, 1674:(C=O) stret. of carbonyl, 1597:(C=N) of imin of oxadiazole ring, 1149:(C-O-C) str. of cyclic ether of the ring. ^{1}H-NMR**:** 0.86 (6H, d, CH_3 (A)), 1.62 (3H, d, CH_3 (B)),1.81 (1 H, m -CH (C)), 2.41 (2H, d - CH_2 (D)), 3.66 (2H, S-CH (E)),3.81 (3H, S-CH3(F)),4.16 (1H, q–CH(G)), 6.72-7.18 (8H, m-Ar-H(H,J,I,K) (Figure 2B).

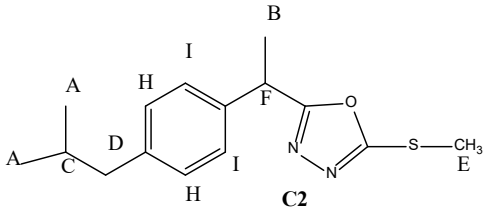
2-(1-(4-isobutylphenyl) ethyl) -5-(methylthio) -1,3,4-oxadiazole) C2)

Yellowish oil, Yield 55%, R*f* = 0,5 (Chlorophorm: ethylacetate 5.5:2.5), IR (v cm^{-1}) :2954,2931:(C-H) asymm. str. of CH_2CH_3, 2870,2840 (C-H) symm.str. Of CH_2CH_3, 1557:(C=N) str. of ring,1157:(C-O-C) str. of cyclic ether of oxadiazole ring.^{1}H-NMR: 0.87(6H, d, CH_3 (A)), 1.62(3H, d, CH_3 (B)), 1.82((1H, m -CH (C)), 2.43(2H, d - CH_2 (D)),2.53(3H, S-CH_3(E)), 4.16(1H, q-CH(F)),7.04-7.18(4H, m-Ar-H(H-I)) (Figure 2C).



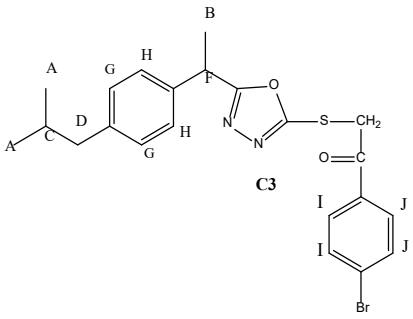
C1

Figure 2A: Synthesis of compound C.



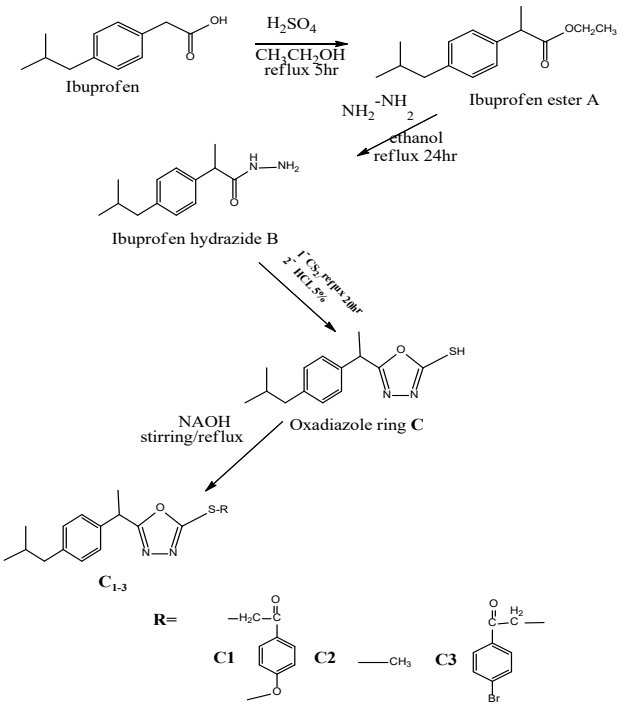
C2

Figure 2B: Synthesis of compound C3



C3

Figure 2C: Synthesis of compound C2



Scheme 1: synthesis of final target compounds(C1-3)

S-(5-(1-(4-isobutylphenyl) ethyl)-1,3,4-oxadiazol-2-yl) 2-(4-bromophenyl) ethanethioate compound C3

Pale brown powder, Yield 65%, R*f* = 0,7 (Chlorophorm: ethylacetate 5.5:2.5), M. P= (145-149). IR (v cm^{-1}): 2954, 2924:(C-H) asymm. str. of CH_2CH_3, 2866, 2853 symm.str. Of CH_2CH_3, 1581: (C=N) str. of ring, 1685: (C=O) str. of carbonyl group,1172: (C-O-C) str. of cyclic ether of oxadiazole ring, 840: (C-Br) str. ^{1}HNMR: 0.87^1(6H, d, CH_3 (A)), 1.62^1(3H, d, CH_3 (B)), 1.82((1H, m -CH (C)), 2.43 (2H, d - CH2 (D)), 3.66 (2H, S-CH_2 (E)), 4.16 (1H, q-CH(F)), 7.04-7.82^1(8H, m-Ar-H(G-J).

Antimicrobial Activity[13]

The^1 target chemicals' antimicrobial ^{1}activity (C, C1-3) was examined using the ^{1}disc diffusion technique against two distinct types of "G + ve"^{1} ^{1}bacteria (*S. aureus* and *S. pyogenes*), "G-ve" bacteria (*K. pneumoniae* and ^{1}*E. coli*), and one ^{1}fungal species (*C. albicans*). ^{1}The activity was measured by measuring the ^{1}zone of inhibition in millimeters with^1 contrast to the stander^1 fluconazole1 as "antifungal^1 agent and^1 ciprofloxacin as "antibacterial agent" and at a concentration of ^{1}100 µg/mL using ^{1}DMSO as a solvent for all of them.

RESULT AND DISCUSSION

Chemistry

The overall synthesis method for the final chemical (C, C1-3) is shown in Scheme 1, which begins with Ibuprofen ethyl ester (A) that made by the reaction of Ibuprofen dissolved in absolute ethanol with the addition of H_2SO_4. The spectrum of ATR-FTIR of compound (A) showed absorption bond at 1731 cm^{-1} due to C=O str. of carbonyl ester and 1160 cm^{-1} due to C-O stretching vibration of ether v*ia* the reflux of compound (A),

Table 1: [1]Anti-microbial 1evaluation of final synthesized compounds (C1-3)

Compound	*The inhibition Zone in mm*					
	Conc. µg/mL	*S. aureus*	*S. pyrogen*	*K. pneumonia*	*E. coli*	*C. albicans*
C	10^3	15	16	15	13	15
C1	10^3	17	16	16	13	16
C2	10^3	13	12	15	-	16
C3	10^3	14	15	13	14	17
Ciprofloxacin		22	25	27	24	
Fluconazole						20
DMSO	[1]Control and solvent					

No activity = (-), slightly active= 1(zone of inhibition between 5–10 mm), moderately active = (zone of inhibition between 10-15 mm), highly active = (zone of inhibition more than 15 mm).

Table 2: The doses and the molecular weight of final compounds

Compounds	*Molecular weight*	*Dose mg/kg*
Ibuprofen	206.29	50
C	262.37	63.59
C1	410.53	99.5
C2	276.4	66.99
C3	459.40	111.34

$p < 0.05$ is considered statistically significant.

hydrazine hydrate in the presence of ethanol yielded product B (Ibuprofen hydrazide). The absorption band at 1684 cm^{-1} for C=O stret. vibration of amide and 3270, 3209 for the stretching vibration of N-H of the hydrazide were visible in the ATR-FTIR spectra of compound B Reflux of 2-(4-lsobutylphenyl) propane hydrazide compound (B) with CS_2 in the presence of KOH in a 50% ethanol-water mixture yielded compound C. The spectra of (ATR-FTIR) for the compound C showed absorption band at 3120:(N-H) str. of thioamide of oxadiazole ring, 3079, 3028 (C-H) str. of Ar-H, 2954, 2931:(C-H) str. of asymm.CH_3.

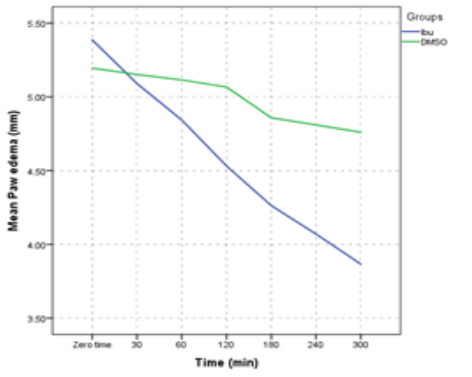


Figure 3: Comparison between the effect of (ibuprofen) reference and the (DMSO) control on paw edema thickness.

CH_2,2908,2866:(C-H) str. of symm.CH_3.CH_2, 1612:(C=N) str. of oxadiazole ring,1516,1462**:(**C=C**)** of Ar ring, 1273**:(**C=S**)** str. of oxadiazole. While the [1]H-NMR **s**pectrum showed singlet at 13.28 SH of oxadiazole. Finally, the compounds(C1-3) were

Table 3: Comparison between the effect of (ibuprofen) reference and the (DMSO) control on paw edema thickness.

Time (min)	*Reference (Ibuprofen) Mean ± STD*	*DMSO*	*p-value*
Zero time	5.38 ± 0.13	5.19 ± 0.28	0.16
30	5.09 ± 0.12	5.15 ± 0.28	0.64
60	4.84 ± 0.21	5.11 ± 0.29	0.09
120	4.53 ± 0.13	5.06 ± 0.29	0.002
180	4.26 ± 0.07	4.85 ± 0.35	0.004
240	4.07 ± 0.10	4.81 ± 0.35	0.0006
300	3.86 ± 0.13	4.76 ± 0.34	0.0002

Table 4: The Effect of DMSO control and target compound on reduction paw edema thickness

Time (Hours)	*Thickness of paw edema in (mm)*				
	DMSO	*C*	*C1*	*C2*	*C3*
Zero time	5.19 ± 0.28a	5.45 ± 0.15a	5.20 ± 0.07a	5.58 ± 0.11a	5.56 ± 0.30a
30	5.15 ± 0.28ab	5.21 ± 0.07b	5.10 ± 0.08ab	5.39 ± 0.11b	5.44 ± 0.27a
60	5.11 ± 0.29ab	5.06 ± 0.09b	5.01 ± 0.08b	5.10 ± 0.18c	4.95 ± 0.44b
120	5.06 ± 0.29ab	4.68 ± 0.08c	4.61 ± 0.07c	4.81 ± 0.17d	4.76 ± 0.23b
180	4.85 ± 0.35ab	4.40 ± 0.11d	4.24 ± 0.06d	4.49 ± 0.15e	4.40 ± 0.17c
240	4.81 ± 0.35ab	4.22 ± 0.31d	3.98 ± 0.14e	4.20 ± 0.12f	3.94 ± 0.25d
300	4.76 ± 0.34b	3.83 ± 0.15e	3.52 ± 0.28f	4.03 ± 0.13f	3.64 ± 0.18d

Table 5: The Effect of DMSO control and target compound on the reduction paw edema thickness

Time (hours)	*Thickness of paw edema in (mm)*				
	Ibuprofen	*C*	*C1*	*C2*	*C3*
Zero time	5.38 ± 0.13a	5.45 ± 0.15a	5.20 ± 0.07a	5.58 ± 0.11a	5.56 ± 0.30a
30	5.09 ± 0.12b	5.21 ± 0.07b	5.10 ± 0.08ab	5.39 ± 0.11b	5.44 ± 0.27a
60	4.84 ± 0.21c	5.06 ± 0.09b	5.01 ± 0.08b	5.10 ± 0.18c	4.95 ± 0.44b
120	4.53 ± 0.13d	4.68 ± 0.08c	4.61 ± 0.07c	4.81 ± 0.17d	4.76 ± 0.23b
180	4.26 ± 0.07e	4.40 ± 0.11d	4.24 ± 0.06d	4.49 ± 0.15e	4.40 ± 0.17c
240	4.07 ± 0.10f	4.22 ± 0.31d	3.98 ± 0.14e	4.20 ± 0.12f	3.94 ± 0.25d
300	3.86 ± 0.13g	3.83 ± 0.15e	3.52 ± 0.28f	4.03 ± 0.13f	3.64 ± 0.18d

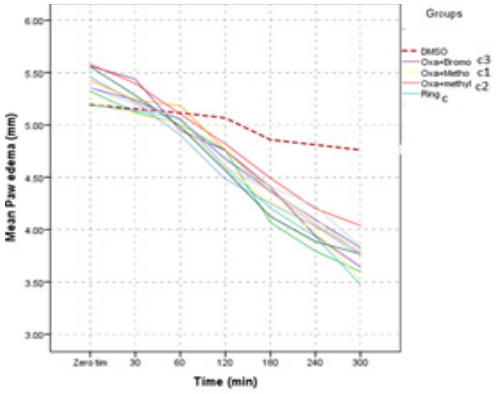


Figure 4: The effect of control (DMSO) and the target compounds on paw edema thickness.

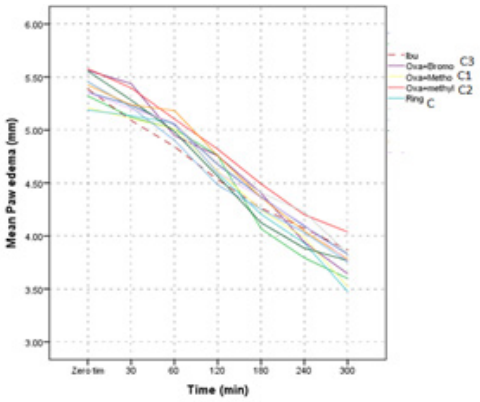


Figure 5: The effect of reference (Ibuprofen) and the target compounds on paw edema thickness.

prepared by the reaction of compound C with different aryl and alkyl halide with addition of NAOH and stirring and or reflexed to yielded the final products. The FTIR spectra show absorption bands at (1581–1674.1) cm^{-1} for C=N stretching of the ring, (1685–1674) cm^{-1} due to C=O str. of carbonyl gropes, (1149–1172) cm^{-1} due to str. of cyclic ether of the ring. ^{1}H-NMR spectra display a singlet at (3.66) due to two protons of CH_2 (-S-CH2-C_6H_5-).

Evaluation of Antimicrobial Activity

The antimicrobial activity of a novel series of synthesized derivatives (C, C,1-3) was tested, and the results in Table (1) demonstrate that many of the final compounds had good activity against [1]both "G-ve" and "G+ve" bacteria. [1]When compared to the other synthesized compounds, compound C showed good anti-[1]bacterial activity for the four species of bacteria, while compound C1 showed the highest antimicrobial activity for "G+ve" bacteria and good activity for "G-ve" bacteria. The compounds (C 2,3) showed moderate activity for both species when compared to the other and to Ciprofloxacin. Compound C2 had no antifungal action against one species of [1]"G-ve" *(E. coli). H*owever,[1]compound C3 has the highest antifungal activity when compared to other synthetic compounds.

The Anti-inflammatory Activity Evaluation

Study of the anti-inflammatory activity of the target compounds was done in Chemistry Analysis Center (CAC), Baghdad, Iraq[1].

An egg white generated paw edema model was used to test the anti-inflammatory properties of the produced products (C, C1-3), and the calculation the reduction of paw thickness is the basis of the evaluation of the anti-inflammatory activity of the expected compound.[14]

The weight of albino rats was approximately (about 180 ± 10 gm). The animals were divided into 13 categories (Six rats in each group), housed by the center in animal houses under regulated conditions.

- **Group 1:** Six rats were used as controls and were given intraperitoneal injections of dimethyl sulfoxide DMSO.[15]
- **Group 2:** Six rats used as reference and were given Ibuprofen in a [1]dose of [1]50 mg/kg[16] dissolved in DMSO.
- **Group C-F:** For each of the four groups (C-F) the rats were injected with one of each of the target compounds (C, C1-3). which dissolved in DMSO. In doses that represent in the Table **2**.

A subcutaneous[1] injection of undiluted[1] egg white (0.1) into the planter[1] side of the rats' hind paw 30 minutes after i.p. administration of the medicines or their carrier caused inflammation. After drug injection, the paw width was measured using a vernier caliper at seven intervals (0, 30, 60, 120, 180, 240, and 300). The data was expressed as a mean ± SEM, and the results were analyzed for statistical significance using an independent t-test to determine significant differences between two groups' means, and a one-way ANOVA and least significant differences (LSD) post hoc test to determine[1] significant differences among groups' means.[17]

DISCUSSION OF THE RESULT

The Comparison of the Effect of (Ibuprofen) Reference Drug Versus Control (DMSO)

There is no significant1difference in paw edema thickness reduction between the reference (ibuprofen) and the control (DSMO) at 0 and 30 minutes, while at 60, 120, 180, 240 and 300 minutes the reference showed significant reduction in the thickness 1of paw edema in comparison with control[1] and as summarized in the Figure 3 and in the Table 3.

The Comparison Effect of the Target Synthesized Compounds Versus Control (DMSO)

The comparison between the target compounds and DMSO (control) showed that there are no significant differences between them at 0 and 30 minutes in the reduction of paw edema thickness. While at 60 to 300 minutes showed a significant difference between the target compounds (C1) and DMSO. The other compounds (C, C2, C3) significantly reduce paw edema thickness from (120–300) minutes compared with DMSO. As summarized in the Figure 4 and Table 4.

The Comparison of the Effect of the Reference (Ibuprofen) with Targets Compounds

The comparison between the target compounds and Ibuprofen(reference) showed that there are no significant differences between them at 0 and 30 minutes. While at 240 to 300 minutes, paw edema thickness was significantly reduced between the target compounds (C, C1, C3) and Ibuprofen. Compared with Ibuprofen, compounds C2 have no significant reduction in paw edema thickness (reference). and as summarized in Figure 5 and Table 5.

CONCLUSION

New series of 5-(1-(4-isobutylphenyl) ethyl)-1,3,4-oxadiazole-2-thiol compound C derivatives were synthesized successfully utilizing current methodologies, and all of the examined compounds were evaluated for antimicrobial and anti-inflammatory activity. All of the final compound's structures were discovered and confirmed (ATR-FTIR and ^{1}H MNR). Antimicrobial testing revealed that compounds C and C1 had the best antibacterial activity, whereas compound C3 had the best antifungal activity. Compared to the other produced compounds and the reference medication, compound C3 had the most anti-inflammatory efficacy compared with other prepared compounds.

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