Ibn Al-Haitham Journal for Pure and Applied Sciences
Journal homepage: jih.uobaghdad.edu.iq
PISSN: 1609-4042, EISSN: 2521-3407
IHJPAS. 2026; 39(3)

Synthesis and Antibacterial Activity of New Hybrid Molecules Containing 1,3,4-Thiadiazole and 1,3,4-Oxadiazole Bearing Ibuprofen Moiety

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Received: 1/February/2026
Accepted: 19/April/2026
Published: 20/July/2026
doi.org/10.30526/39.3.4453

Abstract

A series of novel hybrid molecules containing 1,3,4-oxadiazole and 1,3,4-thiadiazole moieties bearing an ibuprofen moiety were designed, synthesized, and evaluated for their in vitro antibacterial activity against Gram-positive and Gram-negative bacteria. A carboxylic acid compound with a 1,3,4-thiadiazole unit was synthesized via the coupling reaction of 5-(1-(4-isobutylphenyl) ethyl)-1,3,4-thiadiazol-2-amine with benzoic acid. This compound was then used as the starting material to make several new 1,3,4-oxadiazole derivatives through ring closure reactions, after first converting it to its ester (methyl 4-(5-(1-(4-isobutylphenyl)ethyl)-1,3,4-thiadiazol-2-yl) benzoate) and then to the acid hydrazide (4-(5-(1-(4-isobutylphenyl) ethyl)-1,3,4-thiadiazol-2-yl)benzohydrazide). Finally, the intramolecular ring closure of the hydrazide compound with carboxylic acids under reflux in $POCl_3$ afforded 2-(4-(5-(1-(4-isobutylphenyl)ethyl)-1,3,4-thiadiazol-2-yl)phenyl)1,3,4-oxadiazole derivatives. The synthesized compounds were characterized using spectroscopic techniques, including IR, ^{1}H NMR, and ^{13}C NMR. The compounds were tested for antibacterial activity on two Gram-positive (*Streptococcus pyogenes* and *Staphylococcus aureus*) and two Gram-negative (*Escherichia coli* and *Proteus mirabilis*) bacterial strains. The prepared compounds demonstrated significant antibacterial activity compared with Ibuprofen and Ampicillin. The maximum inhibition zones were recorded against *Staphylococcus aureus* (20 mm), *Proteus* (18 mm), *Escherichia coli* (17 mm), and *Streptococcus* (17 mm), suggesting that the synthesized derivatives possess promising antibacterial properties. This difference resulted from substituting the benzene ring with various substituents.

Keywords: Antibacterial, Heterocyclic, Ibuprofen, 1,3,4-Oxadiazole, 1,3,4- Thiadiazole.

1. Introduction

The five-membered ring systems consist of two nitrogen atoms, in addition to either a sulfur atom (thiadiazole) or an oxygen atom (oxadiazole) at positions 1, 3, and 4[1,2]. They demonstrate a wide range of biological activities[3], making them significant in pharmaceutical applications[4]. Their bioactive properties have prompted investigations into their applications as anti-cancer agents[5] and for other therapeutic purposes[6,7]. Also, 1,3,4-oxadiazoles synthesized by Bhardwaj et al. were found to be effective against bacterial strain[8]. Furthermore, Ayash synthesized novel derivatives of 1,3,4-oxadiazole by reacting thiosemicarbazide with tosyl chloride in the presence of pyridine, which also exhibited interesting biological activity and proved effective as antifungal agents[9]. Additionally, Alfraiji and Al-Majidi[10] synthesized new 1,3,4-oxadiazoles that exhibited antimicrobial activity.

Many 1,3,4-thiadiazole derivatives are important in pharmaceutical applications and serve as key intermediates in chemical synthesis. Novel derivatives of 1,3,4-thiadiazole and 1,3,4-oxadiazole were synthesized based on cyclic imides, which exhibited significant antioxidant activity.

Various methods have been established for the synthesis of 1,3,4-oxadiazole and 1,3,4-thiadiazole derivatives[11], including the use of ring closure systems, thioacylhydrazine cyclization, and electrochemical oxidative cyclization[12]. One of the most widely used techniques for creating 1,3,4-oxadiazole derivatives is the reaction of hydrazides with carboxylic acids, aldehydes, or acid chlorides, followed by the cyclization of the resultant acyl hydrazine by the action of a dehydrating agent, such as thionyl chloride ($SOCl_2$)[13], phosphoryl chloride ($POCl_3$)[14], H_2SO_4[15] or (P_2O_5)[16].

The synthesis of 1,3,4-thiadiazole and 1,3,4-oxadiazole heterocyclic compounds via ring-closure reactions is an important method in heterocyclic chemistry[17]. In this way, Kale and co-workers produced 1,3,4-thiadiazoles by treating thiosemicarbazides with strong sulfuric acid. Thiosemicarbazides produced from acid hydrazides react with concentrated sulfuric acid to produce thiadiazoles. This technique emphasizes the applicability of thiosemicarbazide as a precursor for synthesizing thiadiazole rings[18]. In addition to ibuprofen, analogs and related compounds have been developed to enhance efficacy and reduce side effects. This includes Dexibuprofen, the active enantiomer of ibuprofen, along with other structurally analogous NSAIDs like Naproxen, Ketoprofen, Flurbiprofen, and Diclofenac[19]. These compounds exhibit analogous anti-inflammatory and analgesic properties; however, differences in their chemical structures may lead to variations in potency, selectivity, and pharmacokinetic profiles (**Figure 1**). It has been demonstrated that this hybrid technique is successfully used in anticancer, antiviral, and antibacterial drug development[20]. This study aims to synthesize new derivatives of 1,3,4-oxadiazole and 1,3,4-thiadiazole via ring-closure reactions and evaluate their antibacterial activity.

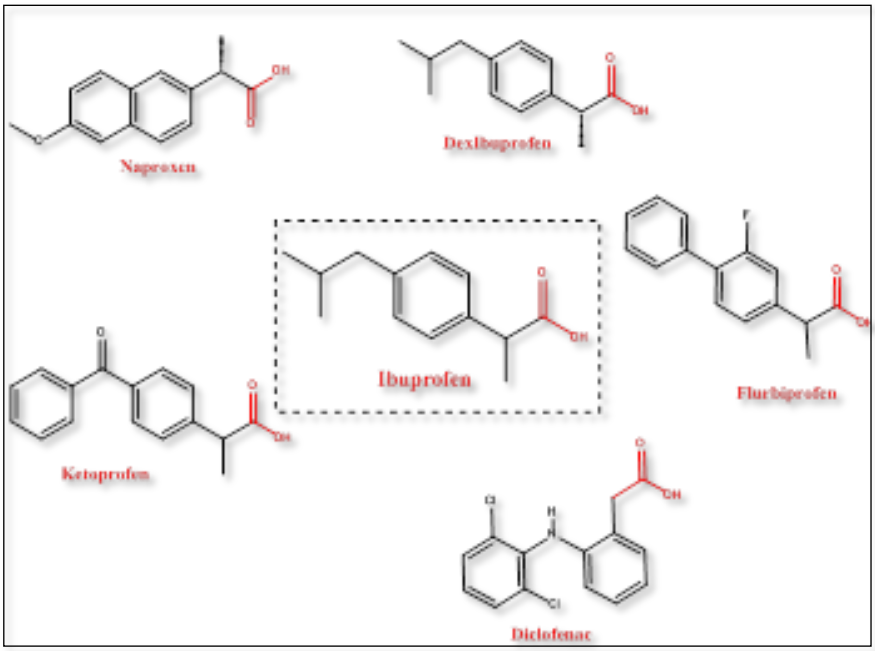


Figure 1. Structures of Ibuprofen and their analogs

2. Materials and Methods

2.1. Instrumentation

All chemicals used in the study were of the highest purity and were used without further purification. The melting points of the synthesized compounds were measured using a Stuart United Kingdom digital melting point apparatus (model Advanced SMP10). IR spectra were obtained using a Shimadzu IR-Spirit FT-IR spectrometer with a QATR-S single-reflection ATR attachment at the Chemistry Department, College of Education for Pure Science, University of Baghdad. The NMR spectra were obtained using a Bruker Ultra Shield 400 MHz spectrometer

(Tehran University Laboratory), with DMSO-d^6 as the solvent and tetramethylsilane (TMS) as the reference.

2.2. Compounds synthesis

2.2.1. Synthesis of 5-(1-(4-isobutylphenyl)ethyl)-1,3,4-thiadiazol-2-amine (1)

About 2.06 g (1.0 mmol) of ibuprofen and 5 mL of phosphorus oxychloride containing 0.91 g (1.0 mmol) of thiosemicarbazide were refluxed for 6 hrs. After cooling the reaction mixture to room temperature, 10 mL of cold water was added carefully. The acidic solution was neutralized with concentrated $NaHCO_3$, resulting in a precipitate that was filtered and washed multiple times with water. The product was recrystallized from ethanol[21], yielding 89% of an off-pale yellow solid with a melting point of 107-109 °C, close to the literature value of 110 °C[22].

2.2.2. Synthesis of 4-(5-(1-(4-isobutylphenyl)ethyl)-1,3,4-thiadiazol-2-yl)benzoic acid (2)

A solution containing 5-(1-(4-isobutylphenyl)ethyl)-1,3,4-thiadiazol-2-amine (75 mmol, 19.6 g) in (120 mL) of water and (40 mL) of concentrated HCl was cooled to 5°C. The mixture was diazotized with 91 mmol (6.2 g) of $NaNO_2$ in 35 mL of water. After 20 minutes, 75 mmol (9.1 g) of benzoic acid in acetone was added to the stirred mixture, followed by 23 mmol (3.91 g) of $CuCl_2 \cdot 2H_2O$ in 25 mL of water.

The reaction was allowed to stand at room temperature for 48 hrs with stirring. Subsequently, the mixture was diluted with 500 mL of water, yielding a pale precipitate, which was filtered, washed with cold water, and purified with ethyl acetate to afford a crystalline compound[23]. Yield 78.6%, brown solid, mp (82-84) °C.

2.2.3.Synthesis of methyl 4-(5-(1-(4-isobutylphenyl)ethyl)-1,3,4-thiadiazol-2-yl)benzoate (3)

A mixture of carboxylic acid (compound 2) (246 mmol, 9.01 g), 100% methanol (101 mL), and pure sulfuric acid (2.6 mL) was refluxed for 6 hrs.

The resulting mixture was cooled and placed on crushed ice, then neutralized with a sodium bicarbonate solution, washed with water, air-dried, and recrystallized from ethyl acetate 24. Yield: 87%, pale brown, mp (68-70) °C.

2.2.4. Synthesis of 4-(5-(1-(4-isobutylphenyl)ethyl)-1,3,4-thiadiazol-2-yl)benzohydrazide (4)

After preparing a solution of ester (compound 3) (30 mmol, 11.4 g) in ethanol (12 mL), pure hydrazine (7.5 mL) was added, and the mixture was refluxed for 5-6 hrs. After this, the reaction mixture was cooled, and the yellow precipitate was filtered, dried, and finally recrystallized from ethyl acetate[22]. Yield 81%, yellow.

2.2.5. Synthesis of oxadiazole compounds (5a-f) (general procedure)

A 0.01 mol (0.38 g) of 4 and 5 mL of phosphorus oxychloride containing 0.01 mol of carboxylic acids were refluxed for 6 hrs. The reaction mixtures were allowed to cool to room temperature, after which 10 mL of cold water was carefully added.

Concentrated $NaHCO_3$ neutralized the acidic solution; the precipitate was filtered, washed several times with water, and recrystallized from ethanol.

Table 1 provides an overview of the physical properties of all synthesized compounds.

Table 1. Physical properties of synthesized compounds

Comp. No.	Nomenclature	Chemical Formula	M.W g/mol	M.P ^{o}C	Yield %	Color
(2)	4-(5-(1-(4-isobutylphenyl)ethyl)-1,3,4-thiadiazol-2-yl)benzoic acid	$C_{21}H_{22}N_2O_2S$	366	82-84	78.6	Brown
(3)	Methyl 4-(5-(1-(4-isobutylphenyl)ethyl)-1,3,4-thiadiazol-2-yl)benzoate	$C_{22}H_{24}N_2O_2S$	380	68-70	87	Dark brown
(4)	4-(5-(1-(4-isobutylphenyl)ethyl)-1,3,4-thiadiazol-2-yl)benzohydrazide	$C_{21}H_{24}N_4OS$	380	-	81	Pale yellow
(5) $_a$	2-(4-(5-(1-(4-isobutylphenyl)ethyl)-1,3,4-thiadiazol -2-yl)phenyl)-5-(4-methoxyphenyl)-1,3,4-oxadiazole	$C_{29}H_{28}N_4O_2S$	496	130	86.5	Brown
(5) $_b$	2-(4-(5-(1-(4-isobutylphenyl)ethyl)-1,3,4-thiadiazol -2-yl)phenyl)-5-phenyl-1,3,4-oxadiazole	$C_{28}H_{26}N_4OS$	466	117-119	79.2	Dark brown
(5) $_c$	2-(4-chlorophenyl)-5-(4-(5-(1-(4- isobutylphenyl) ethyl)-1,3,4-thiadiazol-2-yl)phenyl)-1,3,4-oxadiazole	$C_{28}H_{25}ClN_4OS$	501	108-110	82	white
(5) $_d$	4-(5-(4-(5-(1-(4-isobutylphenyl)ethyl)-1,3,4-thiadiazol-2-yl)phenyl)-1,3,4-oxadiazol-2-yl)aniline	$C_{28}H_{27}N_5OS$	481	114-116	89.1	Yellow
(5) $_e$	2-(1-(4-isobutylphenyl)ethyl)-5-(4-(5-(1-(4-isobutylphenyl)ethyl)-1,3,4-thiadiazol-2-yl)phenyl)-1,3,4-oxadiazole	$C_{40}H_{42}N_4OS$	662	133-135	73	White
(5) $_f$	2-(4-(5-(1-(4-isobutylphenyl)ethyl)-1,3,4-thiadiazol-2-yl)phenyl)-5-(p-tolyl)-1,3,4-oxadiazole	$C_{29}H_{28}N_4OS$	480	121-123	83.4	Brown

2.3 Evaluation of anti-microbial activity

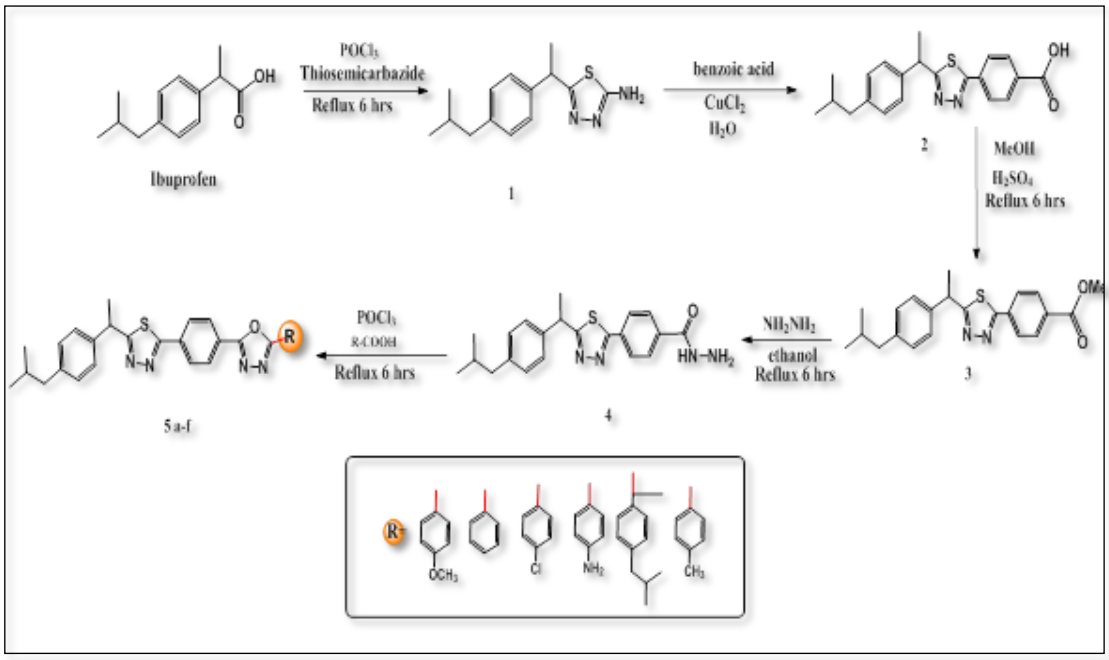
The antibacterial activity of all synthesized compounds was tested in vitro against two Gram-positive bacteria, *Streptococcus pyogenes* and *Staphylococcus aureus*, and two Gram-negative bacteria, *Escherichia coli* and *Proteus mirabilis*. These strains were chosen for their clinical relevance and known resistance to common antibiotics, which can pose serious health risks[25]. Antibacterial activity was measured using the agar well diffusion method on Muller-Hinton Agar. The compounds were dissolved in DMSO, which also served as a negative control. The MacFarland method was used to assess antibacterial activity[26]. The effectiveness of the compounds was further evaluated with the broth microdilution technique. Bacterial inocula were standardized to a 0.5 McFarland turbidity standard, corresponding to approximately 1.5×10^8 CFU/mL. Fresh colonies were suspended in sterile saline and adjusted to the same standard. The suspension was then diluted in Mueller–Hinton broth to reach a final concentration of about 5×10^5 CFU/mL in each well. Ampicillin was used as a reference antibiotic for comparison. After inoculating the bacterial cultures, the plates were incubated at 37°C for 24 hours. The antibacterial efficacy of each drug was evaluated by measuring the inhibition zone in millimeters surrounding each well. Heightened inhibition zones were associated with enhanced antibacterial activity in some cases compared with the standard drug.

3. Results

Initially, 5-(1-(4-isobutylphenyl)ethyl)-1,3,4-thiadiazol-2-amine compound (1) was synthesized in good yields through the reaction of the corresponding ibuprofen with thiosemicarbazide in the presence of phosphorus oxychloride. Compound (1) was converted to biphenyl carboxylic acid via diazotization, followed by coupling with benzoic acid to form Compound (2). The acid compound (2) was identified by FTIR and NMR. The FTIR spectra displayed the appearance of a new band at (3420-2550) cm^{-1}, 1687 cm^{-1}, and 1288 cm^{-1} due to stretching vibration of O-H, C=O, and C-O, respectively, of the carboxylic moiety[23]. ^{1}HNMR spectra of this compound revealed a characteristic singlet signal at δ 9.44 ppm for one proton of

the OH group. Also, the ^{13}C-NMR spectrum showed a signal at 175.96 ppm for C=O. By the esterification reaction of compound (2) in methanol and H_2SO_4 medium, methyl 4-(5-(1-(4-isobutylphenyl)ethyl)-1,3,4-thiadiazol-2-yl)benzoate (compound 3) is obtained. The IR spectrum showed two new bands for the ester group at 1734 cm^{-1} for the C=O ester and 1271 cm^{-1} for C-O [27]. The ^{1}H-NMR spectrum gives a new singlet signal at δ 3.87 ppm related to OCH_3 protons. The ^{13}C NMR spectrum of the compound showed a new signal at 181.97 ppm for the C=O ester. The 4-(5-(1-(4-isobutylphenyl)ethyl)-1,3,4-thiadiazol-2-yl)benzohydrazide (compound 4) was synthesized from the corresponding ester by treatment with hydrazine hydrate in ethanol. The IR spectrum showed new bands for C=O amide at 1658 cm^{-1} and 3297-3151 cm^{-1} for N–H and NH_2. The ^{1}H-NMR spectrum gives two new singlet signals at δ 9.83 ppm and δ 4.70 ppm related to NH and NH_2 protons.

The ^{13}C NMR spectrum of the compound showed a new signal at 173.46 ppm for the C=O amide. Finally, the intramolecular ring closure of hydrazide compound (4)with carboxylic acids, under reflux in $POCl_3$ for 6 hours, afforded 2-(4-(5-(1-(4-isobutylphenyl)ethyl)-1,3,4-thiadiazol-2-yl)phenyl)1,3,4-oxadiazole derivatives compounds (5_{a-f}), as shown in **Scheme 1.**



Scheme 1. Synthetic route of compounds [1-5]

Spectroscopic methods confirmed the structures of the new derivatives: FT-IR (**Tables 2** and **3**), ^{1}H NMR, and ^{13}C NMR (**Table 4)**.

Table 2. The FT-IR spectra of the synthesized compounds (2-4) in (cm^{-1})

Comp. No.	(C-H) Arom.	(C-H) Aliph.	(C=O)	(C=N)	(C=C)	(C-O)	Other
(2)	3066	2954–2869	1687	1637	1584	1288	(br, O-H str) 3420–2550
(3)	3060	2954–2868	1734	1610	1510	1271	–
(4)	3047	2954–2868	1658	1608	1571	1242	(NH_2 Str) 3297, 3151

Table 3. The FT-IR spectra of the synthesized compounds (5_{a-f}) in (cm^{-1})

Comp. No.	(C-H) Arom.	(C-H) Aliph.	(C=N)	(C=C)	Other
(5) $_a$	3025	2953–2842	1665,1611	1584	–
(5) $_b$	3045	2954–2862	1665,1602	1551	–
(5) $_c$	3050	2955–2869	1644,1615	1598	–
(5) $_d$	3080	2955–2868	1660,1607	1600	(NH_2 Str) 3330-3319
(5) $_e$	3025	2954–2888	1677,1640	1510	–
(5) $_f$	3026	2953–2867	1645,1610	1579	–

Table 4. The chemical shift of the synthesized compounds (2-5)

Comp.	^{1}H-NMR δ (ppm)	^{13}C-NMR δ (ppm)
(2)	9.44 s (1H, OH), 7.97–7.06 m (8H, H_{Ar}), 4.45 q (1H, CHCH$_3$, *J* 7.1), 2.39 d (2H, CH$_2$CH, *J* 6.9), 1.85–1.50 m (1H, CHMe$_2$), 1.35 d (3H, CHCH$_3$, *J* 7.1), 0.84 d (6H, 2CH$_3$, *J* 6.6)	CH$_3$:19.01 ; CH: 20.50; CH$_3$: 22.62; CH$_2$: 30.10 ; CH : 44.69, 44.75; CH$_{Ar}$: 127.5-160.3; C=N: 167.79; C=O: 175.96
(3)	7.99 –7.03 m (8H, H_{Ar}), 4.34 q (1H, CHCH$_3$, *J* 6.7), 3.87 s (3H, OCH$_3$), 2.41 d (1H, CHCH$_3$, *J* 6.1), 1.71–1.51 m (1H, CHMe$_2$), 1.37 d (3H, CHCH$_3$, *J* 7.2), 0.84 d (6H, 2CH$_3$, *J* 6.6)	CH$_3$: 12.11; CH: 21.43; CH$_3$: 22.64; CH$_2$: 30.11; CH :44.67; OCH$_3$: 63.12; CH$_{Ar}$: 127.3-159.38 ; C=N: 168.20; C=O: 181.97
(4)	9.83 s (1H, NH), 7.88–7.06 m (8H, H_{Ar}), 4.70 br s (2H, NH$_2$), 4.33 q (1H, CHCH$_3$, *J* 6.9), 2.38 d (2H, CH$_2$CH, *J* 7.1), 1.74–1.52 m (1H, CHMe$_2$), 1.32 d (3H, CHCH$_3$, *J* 7.2), 0.81 d (6H, 2CH$_3$, *J* 6.4)	CH$_3$: 18.82; CH: 21.43; CH$_3$: 22.62; CH$_2$: 30.10 ; CH : 44.68 ; CH$_{Ar}$: 127-163.1 C=N: 169.06, C=O: 173.46
(5) $_a$	7.90–6.86 m (12H, H_{Ar}), 4.20 q (1H, CHCH$_3$, *J* 7.1), 3.63 s (3H, OCH$_3$), 2.10 d (2H, CH$_2$CH, *J* 6.8), 1.52–1.42 m (1H, CHMe$_2$), 1.32 d (3H, CHCH$_3$, *J* 7.3), 0.80 d (6H, 2CH$_3$, *J* 6.6)	CH$_3$:19.04; CH: 22.63; CH$_3$:22.66; CH$_2$: 30.07; CH$_2$: 44.65; OCH$_3$: 63.12; CH$_{Ar}$: 127 -162.4 ;C=N: 162.45
(5) $_b$	8.0–7.06 m (13H, H_{Ar}), 4.33 q (1H, CHCH$_3$, *J* 7.2), 2.40 d (2H, CH$_2$CH, *J* 7.1), 1.85–1.54 m (1H, CHMe$_2$), 1.23 d (3H, CHCH$_3$, *J* 7.4), 0.86 d (6H, 2CH$_3$, *J* 6.3)	CH$_3$:19.05 ; CH: 21.42; CH$_3$: 22.64 ; CH:30.10 ; CH$_2$: 44.66; CH$_{Ar}$: 123.1-143 ;C=N: 164.52
(5) $_c$	8.17–7.07 m (12H, H_{Ar}), 4.30 q (1H, CHCH$_3$, *J* 6.6), 2.39 d (2H, CH$_2$CH, *J* 7.1), 1.77–1.30 m (1H, CHMe$_2$), 1.22 d (3H, CHCH$_3$, *J* 7.1), 0.80 d (6H, 2CH$_3$, *J* 7.2)	CH$_3$:12.53 ; CH:14.18, ; CH$_3$:22.62 ; CH:30.06; CH$_2$: 44.65; CH$_{Ar}$: 127.1-153.4 ; C=N: 164.78
(5) $_d$	8.10–7.07 m (12H, H_{Ar}), 4.34 q (1H, CHCH$_3$, *J* 7.1), 6.74 s (2H, NH$_2$), 2.42 d (2H, CH$_2$CH, *J* 6.6), 1.74–1.52 m (1H, CHMe$_2$), 1.24 d (3H, CHCH$_3$, *J* 6.5), 0.86 d (6H, 2CH$_3$, *J* 7.2)	-
(5) $_e$	7.63–6.80 m (12H, H_{Ar}), 4.12 q (1H, 2CHCH$_3$, *J* 6.8), 2.31 d (4H, 2CH$_2$CH, *J* 7.2), 1.60–1.04 m (1H, 2CHMe$_2$), 0.91 d (6H, 2CHCH$_3$, *J* 6.6), 0.60 d (12H, 4CH$_3$, *J* 6.9)	CH$_3$:17.25 ;CH:20.17, ; CH$_3$:22.64; CH: 29.51, CH$_2$: 43.27; 44.67 ; CH$_{Ar}$: 127.3-154.2 ;C=N: 173.02
(5) $_f$	8.15–7.09 m (12H, H_{Ar}), 4.35 q (1H, CHCH$_3$, *J* 7.1), 2.41 s (3H, CH$_3$), 2.37 d (2H, CH$_2$CH, *J* 7.3), 1.84–1.51 m (1H, CHMe$_2$), 1.12 d (3H, CHCH$_3$, *J* 7.1), 0.84 d (6H, 2CH$_3$, *J* 7.2)	CH$_3$:21.63; CH: 22.63; CH: 30.09; CH$_2$: 44.64; CH$_{Ar}$: 121.5-142.9 C=N: 164.57

The FT-IR spectra showed two significant bands in the range (1665-1644) cm^{-1}, and (1178-1120) cm^{-1}, which could be attributed to the stretching vibration of the C=N and C-O-C, respectively, of the oxadiazole ring. Also showed the disappearance of absorption bands corresponding to C=O, N–H, and NH_2 in the starting materials. The ^{1}H-NMR spectra of (5a-f) indicate the disappearance of signals for NH, NH_2, and OH protons of the starting materials.

3.1 Anti-microbial activity

The inhibition zone diameters presented in **Table 5** were consistent with the reference values reported for ampicillin[28].

The antimicrobial screening results showed that ibuprofen did not produce an inhibition zone against *E. coli*, which aligns with previous studies[29–31] suggesting that ibuprofen has no direct antibacterial effect against Gram-negative bacteria. In this study, the prepared compounds (1-5), except 5c, showed greater antibacterial activity than the original substance (Ibuprofen) against *Escherichia coli* (Gram-negative). Synthesized compounds demonstrated inhibition zones against *Staphylococcus aureus* (20 mm), *Proteus* (18 mm), *Escherichia coli* (17 mm), and *Streptococcus* (17 mm).

Table 5. Diameter of inhibition zones (mm) produced by (1-5) against *Escherichia coli*, *Streptococcus pyogenes*, *Staphylococcus aureus*, and *Proteus mirabilis*

Compound	Zone of inhibition in (mm)			
	Gram negative		Gram positive	
	E. coli	***Protus.***	***Staph.***	***Strep.***
Ibuprofen	-	15	15	22
1	15	17	-	-
2	17	15	17	15
3	12	12	12	16
4	15	18	20	15
5a	17	-	12	-
5b	16	-	15	14
5c	-	-	-	-
5d	14	12	12	-
5e	13	12	12	-
5f	15	14	-	14
Ampicillin	14	13	14	18
DMSO	-	-	-	-

4. Discussion

The synthetic approach enabled the efficient preparation of new hybrid molecules containing 1,3,4-oxadiazole and 1,3,4-thiadiazole bearing an Ibuprofen moiety in a series of clear steps. The 1,3,4-thiadiazole core was an important intermediate that enabled further modifications to generate a variety of heterocyclic structures. Data from FT-IR, ^{1}H-NMR, and ^{13}C-NMR analyses consistently confirmed that the functional groups were successfully converted at each stage.

The FT-IR spectra showed clear carbonyl, ester, amide, and heterocyclic absorption bands, while the NMR spectra displayed matching proton and carbon signals. These results confirmed the structure of the new 1,3,4-thiadiazole and 1,3,4-oxadiazole compounds. The loss of NH_2 signals and the appearance of new NH signals strongly indicated that cyclization was successful in the final step. However, these results show that the synthetic method was reliable and led to the successful synthesis of the two target heterocyclic compounds.

The synthesized compounds exhibited varying effects against the tested bacteria (*Streptococcus pyogenes*, *Staphylococcus aureus*, and *Proteus mirabilis*). This could be because the outer membrane of Gram-negative bacteria makes it difficult for them to enter the body, or it could be attributed to the varying substitution of the benzene ring with different groups[32].

Conclusion

The synthesis of five new-membered hybrid heterocyclic compounds containing both 1,3,4-oxadiazole and 1,3,4-thiadiazole bearing the ibuprofen moiety was carried out in five stages. These compounds were characterized using various spectroscopic methods and tested against multiple bacterial species. The synthesized derivatives showed good efficacy compared with the reference drugs Ibuprofen and Ampicillin, suggesting they could be promising antibacterial agents.

Acknowledgment

The authors thank the College of Education for Pure Science (Ibn Al-Haitham) for their assistance and support in this study.

Conflict of Interest

The authors declare that they have no conflicts of interest.

Funding

The researchers did not receive any funding.

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