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Synthesis, Characterization, and Preliminary Pharmacological Evaluation of New Naproxen Containing 1,3,4-thiadiazole-2-thiol Derivatives

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Abstract

In this research, a novel group of 1,3,4-thiadiazol-2-thiol derivatives was synthesized based on naproxen. The process involved esterifying the carbonyl group of naproxen using thionyl chloride and methanol, followed by the creation of naproxen hydrazide, then the use of CS2 and basic medium to convert naproxen hydrazide to the potassium salt of dithiocarbazate. Further oxidation with concentrated sulfuric acid resulted in a compound containing the thiol thiadiazole ring. Subsequently, the final compounds (Gh1, Gh2, Gh3, and Gh4) were produced through an alkylation reaction. These compounds were identified using infrared spectroscopy and proton nuclear magnetic resonance. The anti-inflammatory efficacy was then assessed in vivo by inducing acute inflammation in laboratory rats using egg whites. The compounds were successfully synthesized with a percentage yield approaching 70%, and it was discovered that they are effective in reducing the thickness of the paw edema of the tested rats and have an anti-inflammatory influence similar to the effect of the reference substance (naproxen). Some compounds were more effective than naproxen at some trial times, such as compound (Gh1) at the time (T7) after five hours of practical experience.

Keywords: NSAIDs, 1,3,4-Thiadiazole, Heterocyclic Compounds, Naproxen, Pharmacological Evaluation, Synthesis, Characterization.

Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly utilized pharmaceuticals globally for the treatment of fever, pain, and inflammation associated with various diseases. [(1)]

Despite their potent anti-inflammatory, analgesic, and antipyretic capabilities, they also raise the risk of serious side effects such as cardiac failure, renal failure, and gastrointestinal problems [(2)]. As a result, it is critical to identify anti-inflammatory drugs that do not cause ulcers. [(3-5)]

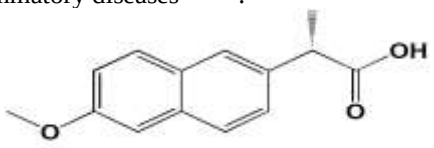
NSAIDs act by blocking cyclooxygenases (COX) enzymes [(6-8)], which are required for the formation of prostaglandin H2 (PGH2) [(9-11)]. Pain, swelling, and inflammation are caused by prostaglandins, which are generated in response to an injury or specific disorders. [(12, 13)]

COX-1 is abundantly expressed in the kidneys and gastrointestinal linings, where it helps maintain homeostasis. It also plays an important function in platelet aggregation. COX-2, on the other hand, is only present during an inflammatory reaction, resulting in the release of prostanoids, mitogens, and cytokines. [(14,15)]

Naproxen is a well-known nonsteroidal anti-inflammatory medicine from the aryl propanoic acid family [(16)]. For more than forty years, naproxen has been used to treat rheumatoid arthritis, pain, inflammation, and fevers [(13)]. Naproxen is commonly utilized because of its wide range of applications; it non-selectively inhibits the primary COX isoforms. [(17)] This might cause some of the associated adverse effects, including gastrointestinal irritation unintentionally. [(18, 19)], hyperacidity, nausea, heartburn, bruises, ulcerative features, headache, bleeding, itchy skin, and so on [(20)]. Although Naproxen's pharmacological effects are attributed to its carboxylic acid (COOH) group, this same group is also accountable for several adverse reactions, such as gastrointestinal irritation and ulcers, when the medication is ingested orally. Therefore, altering the COOH group through processes like esterification, amide formation, or salt formation can reduce acidity levels, thereby minimizing gastrointestinal irritation and lowering the likelihood of interaction with stomach lining receptors. This modification can potentially impact the drug's solubility and absorption characteristics, enhance the drug's selectivity for the target enzyme COX-2 over COX-1, and influence side effect profiles without compromising efficacy. [(21-24)]

On the whole, adjusting the COOH group in naproxen can serve as a strategy to enhance the

drug's therapeutic index, improving its effectiveness while decreasing the frequency and intensity of side effects Nonetheless, it is crucial to emphasize that any alterations must be thoroughly examined and assessed to ensure that they do not jeopardize the drug's efficacy or safety profile. Recent studies have shown that structurally modifying naproxen has opened up new therapeutic processes for the treatment of inflammation and inflammatory diseases [25-28].



(*S*)-naproxen

Heterocyclic compounds are characterized by having the highest number of conjugated double bonds and containing one or multiple heteroatoms (like oxygen, nitrogen, or sulfur) alongside carbon and hydrogen. [29, 30] Heterocyclic chemistry is a fast-emerging subfield of organic chemistry. In 1998, approximately 60% of all synthesis was heterocyclic. [31]

Many various domains currently publish new heterocyclic compounds, including biology, materials science, and medicine.[32] Numerous compounds having a heterocyclic ring of five members have extraordinary chemical properties and perform a wide range of biological functions. [33]

Based on findings from published studies, 1,3,4-thiadiazole derivatives are considered the most hopeful group of molecules with the potential for therapeutic effectiveness. [34]. Compounds from the 1,3,4-thiadiazole derivative group have been shown in studies to exhibit antibacterial, antifungal, [35] antitubercular [36], anti-inflammatory, analgesic, antipsychotic, anticonvulsant, antidepressant, and anti-leishmanial properties. Several published studies have demonstrated the anti-cancer effects of these substances. [37, 38]

The diversity of biological actions exhibited by 1,3,4-thiadiazole derivatives is attributed to the aromatic nature of the ring. It also gives the five-membered ring structure remarkable in vivo stability and low toxicity to higher animals, including humans. [39]

Materials and Methods

Hyper-chem Company (China) and Pioneer Co. for the pharmaceutical industries supplied naproxen compound. The solvents, additional chemical components (ethyl acetate, ethanol, hexane, toluene, thionyl chloride, methanol, hydrazine hydrate, concentrated H_2SO_4), and other chemicals required were obtained from commercial vendors for use in the synthesis.

Wear the proper personal protective equipment (PPE) while handling dangerous chemicals like thionyl chloride and hydrazine hydrate. Examples of PPE include gloves, a face shield, lab coats, safety goggles, and closed-toe shoes.

Thin layer chromatography (TLC; GF254, Merk, Germany) used UV light (254 nm) to monitor reactions and verify product purity. A: [benzene: chloroform: ethyl acetate (5:4:1)] and B: [hexane: ethyl acetate (5.8:4.2)] were the two solvent systems used (by trial). Melting points were determined without correction using the Stuart SMP3 melting point equipment in open capillary tubes. At the University of Baghdad's College of Pharmacy, FT-IR spectra were produced using a Japanese Shimadzu FT-IR spectrophotometer. At Mashhad University of Medical Sciences, ^{1}H-NMR was done at 300 MHz with a Brucker ultrashield model with DMSO-d6 as the solvent. Chemical shifts were expressed as (ppm).

Synthesis of Naproxen methyl ester: methyl (S)-2-(6-methoxynaphthalen-2-y l)propanoate (comp. 1)

In a (250-ml) round-bottom flask, cool (50 ml) of dry methanol and (5 g,21.7mmol) of Naproxen to approximately (-5 ˚C) in an ice bath with vigorous stirring, add thionyl chloride (2. ml, 27.56mmol) drop by drop while stirring.

The interaction of thionyl chloride ($SOCl_2$) with methanol (CH_3OH) is extremely exothermic, resulting in the release of a considerable quantity of heat. Accurate temperature regulation is essential for various purposes: preventing uncontrolled reactions, managing product generation, and guaranteeing safety.

Following the addition, the mixture was heated to 40˚C and stirred for three hours. The mixture was then refluxed for 3-4 hours at 75 ˚C before being left to reach room temperature, and then the solvent was evaporated under reduced pressure.

The precipitated material was re-dissolved in dry methanol and evaporated several times under reduced pressure to eliminate excess thionyl chloride. The product was dissolved in dry ether with the addition of a 10% aqueous solution of sodium bicarbonate $NaHCO_3$, by using a 100-mL separating funnel to separate the organic layer. Finally, the solvent was evaporated under reduced pressure, resulting in a whitish material that was crystallized again using absolute ethanol. [9, 40, 41]

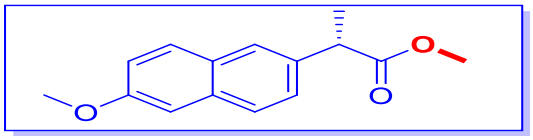


Figure 1. chemical structure of methyl (S)-2-(6-methoxynaphthalen-2-y l) propanoate (comp. 1)

Synthesis of Naproxen hydrazide: (S)-2-(6-methoxynaphthalen-2-yl) propanehydrazide (comp.2)

In a 250-ml round-bottom flask, Naproxen methyl ester (5 g, 20.45 mmol) was weighed, hydrazine hydrate (16 ml, 347.65 mmol, 99.5%) was then added dropwise.

Hydrazine hydrate acts as a potent reducing agent and has the potential to undergo violent reactions with different substances. It is crucial to exercise caution during its addition to prevent such reactions, which may result from rapid addition or temperature changes leading to decomposition. Regulating the temperature is essential in reducing the likelihood of hazardous reactions, thus promoting safe handling and stability during the entire process.

Followed by stirring with heat for 15 minutes. A minimal amount of absolute ethanol (20-30 ml) was added, and the mixture was refluxed for 8 hours at 80 ˚C, resulting in a clear yellow solution within half an hour. After the reaction, the solution was allowed to cool to room temperature, followed by the addition of dry ether and filtration.

Post-filtration, 20 milliliters of cold distilled water were introduced to precipitate the product, which was then dried. The resulting precipitate was further crystallized using ethanol. (42-45).

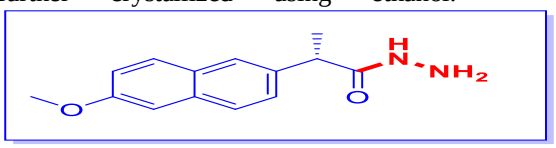


Figure 2. chemical structure of methyl (S)-2-(6-methoxynaphthalen-2-y l) propanoate (comp. 2)

Synthesis of potassium salt of dithiocarbazate (comp. 3)

In a 100-ml round flask, dissolve (1 g, 4.09 mmol) of naproxen hydrazide in absolute ethanol. Subsequently, introduce (0.46 g, 8.18 mmol) of potassium hydroxide to the solution following its dissolution in absolute ethanol. The reaction flask is then placed in an ice bath to lower the temperature to around (-4 ˚C) and stirring is continued. CS2 (0.49 ml, 8.18 mmol) is added dropwise to the mixture while vigorously stirring, and the reaction is allowed to proceed for 2 hours, resulting in a cloudy suspension. Finally, cold dry ether is poured in to precipitate the product, which is then filtered and washed with ether. (46, 47)

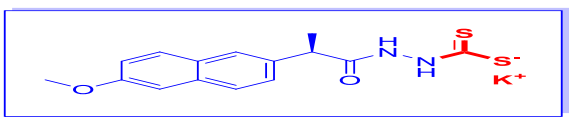


Figure 3. chemical structure of potassium (S)-2-(2-(6-methoxynaphthalen-2-yl) propanoyl) hydrazine-1-carbodithioate(comp.3)

Synthesis of 1,3,4-thiadiazole -2-thiol(comp.4)

Transfer 5 ml of concentrated sulfuric acid (cold, 0-2 ˚c) into a 50-ml round flask and place it in an ice bath. Then introduce 1 g of powdered compound (3) into the flask while stirring rapidly and adding small increments. The temperature was kept within the range of 6-8 ˚C as the solid dissolved swiftly within this interval. Once the addition was finished, stirring was resumed for a duration of 5 to 8 minutes, resulting in a yellow solution yield.

Subsequently, the reaction is ceased by adding moderate amounts of ammonia (strong exothermic reaction). The solution transitions into a suspension and is poured into ice water while being continuously stirred. Afterward, the precipitate is filtered, rinsed multiple times with distilled water, and allowed to dry in the preparation for recrystallization using aqueous ethanol. (46, 48, 49)

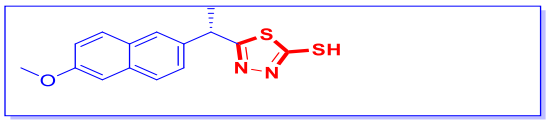


Figure 4. chemical structure of (S)-5-(1-(6-methoxynaphthalen-2-yl)ethyl)-1,3,4-thiadiazole-2-thiol, (comp.4)

Synthesis of 1,3,4-thiadiazole -2-thiol derivatives(Gh1-4)

In a 250-ml round flask, dissolve (0.3 g, 1 mmol) of (comp. 4) in 20 ml of ethanol. Subsequently, introduce (0.3 ml, 2 mmol) of triethylamine, and under continuous stirring, sequentially incorporate (1.2 mmol) from each of the substituted groups, including: (0.33 g) 4-bromphenacyl bromide (for compound Gh1), (0.14ml) benzyl chloride (for compound Gh2), (0.25 g) 4-bromobenzylchloride (for compound Gh3), and (0.15ml) 4-methoxybenzyl chloride (for compound Gh4).

Raise the temperature to 80 ˚c to initiate a reflux reaction lasting two hours. Subsequently, turn off the heat and stir for an additional 4 hours. Allow the reaction mixture to cool to room temperature, then quench it with distilled water. Extract the product using ethyl acetate (3*50 ml) and wash the combined organic layer with brine (50 ml). Dry the organic layer using anhydrous sodium sulfate (20 g), filter it, and evaporate the solvent under reduced pressure to obtain the crude product. Recrystallize the crude product with aqueous ethanol. (50, 51)

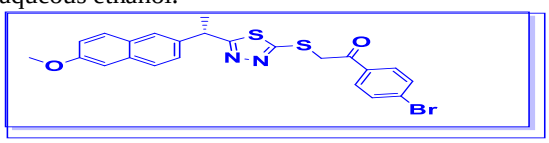


Figure 5. chemical structure of (S)-1-(4-bromophenyl)-2-((5-(1-(6-methoxynaphthalen-2-yl)ethyl)-1,3,4-thiadiazol-2-yl)thio)ethan-1-one(compound Gh1)

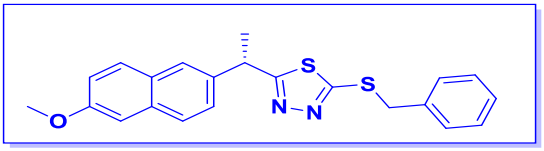


Figure 6. chemical structure of (S)-2-(benzylthio)-5-(1-(6-methoxynaphthalen-2-yl) ethyl)-1,3,4-thiadiazole (compound Gh2)

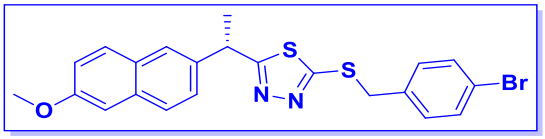


Figure 7. chemical structure of (S)-2-((4-bromobenzyl) thio)-5-(1-(6-methoxynaphthalen-2-yl) ethyl)-1,3,4-thiadiazole (compound Gh3)

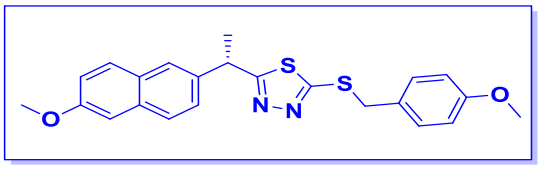
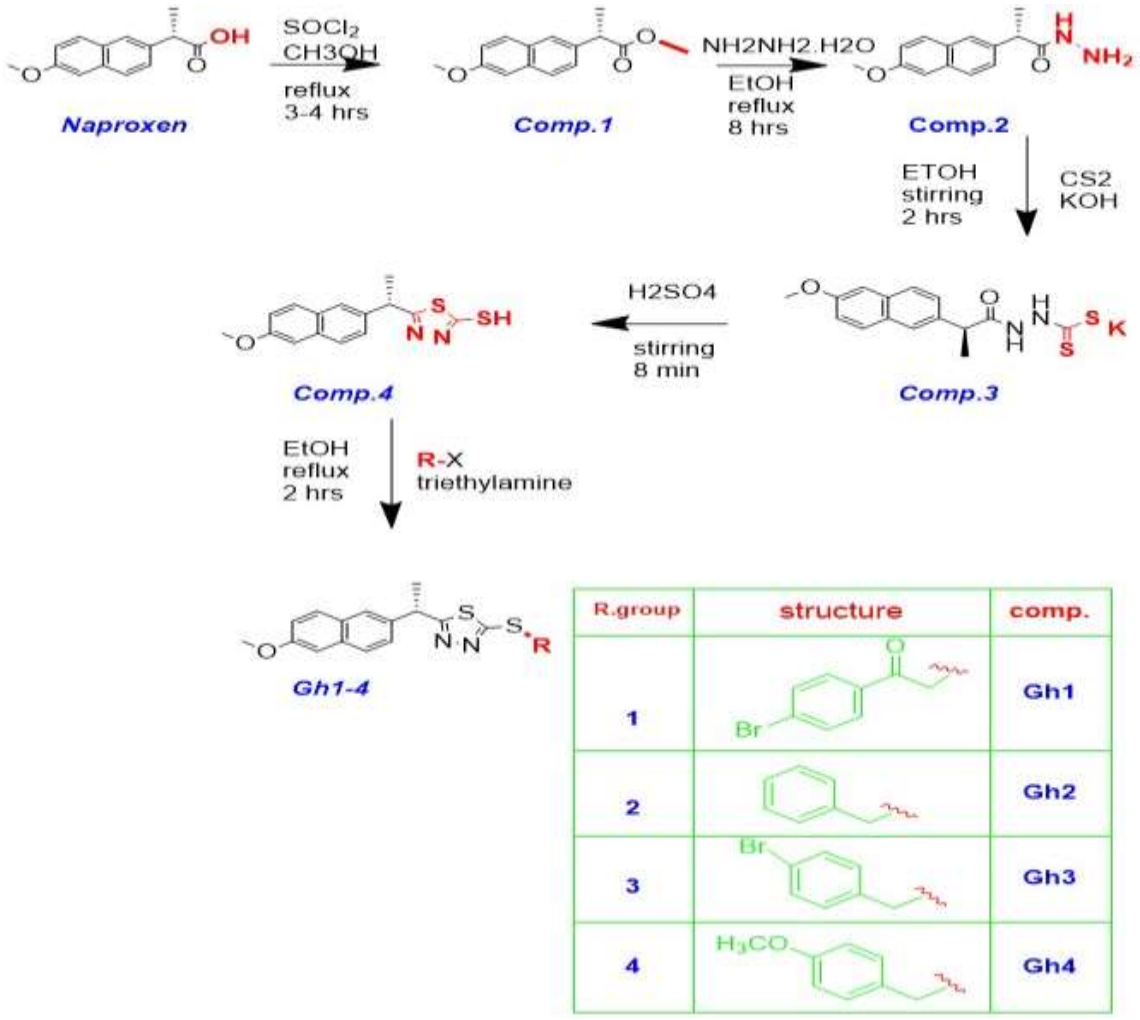


Figure 8. chemical structure of (S)-2-((4-methoxybenzyl) thio) – 5 - (1 - (6 -methoxynaphthalen-2-yl) ethyl) -1 , 3 , 4 - thiadiazole (compound Gh4)

The synthetic procedures for 1,3,4-thiadiazole-2 thiol derivatives (Gh1-4) are clearly depicted in Scheme (1), with detailed information on the characterization of these compounds and their intermediates, including percent yields, melting points, and Rf values as listed in Table (2). The identification of functional groups in all synthesized compounds was conducted via FT-IR spectroscopy, with findings detailed in Table (3). Moreover, the chemical structures of the final compounds were validated through ^{1}HNMR spectroscopy, as indicated in Table (4) .



Scheme 1. Synthesis of 1,3,4-thiadiazole -2-thiol derivatives compounds.

Anti-inflammatory activity

The generated compounds (Gh1, Gh2, Gh3, and Gh4) were tested for anti-inflammatory effects *in vivo* using the egg-white induced paw edema method, which assesses the decrease in paw thickness. Those results were then compared to the anti-inflammatory capabilities of naproxen (as a reference) and DMSO (a control).

The methods for anti-inflammatory study [52, 53]

investigated the intended compound's anti-inflammatory effects researched at the University of Karbala College of Pharmacy in Karbala, Iraq.

The albino rats weighed approximately 1٧0–215 grams. The animals were housed in animal houses, segregated by sex (each group included six rats), and placed in the same area under uniform conditions. The animals were given free access to water and commercial food.

Group 1: Six rats acted as the control group and received intraperitoneal (IPE) injections, at a dosage (2 ml/kg) of dimethyl sulfoxide (DMSO).

Group 2: Naproxen was given to six rats as reference animals at a dosage (10 mg/kg) dissolved in dimethyl sulfoxide.

Groups 3-6: The rats were injected with specific substances from all four groups (Gh1, Gh2, Gh3, and Gh4). Which DMSO was dissolved.

Inflammation was induced by injecting 0.1 ml of undiluted egg white into the plantar side of the rats' hind paws 30 minutes after (IPE) administering medical products or their carriers. Following the substance's injection, the breadth of the paw was measured with a Vernier caliper at seven different intervals (0, 30, 60, 120, 180, 240, and 300 minutes).

Determination of Dose: The dosages of the synthesized target compounds (Table 1) were determined using the following general formula below, while the naproxen dose was given at 10 mg/kg.

Dose of reference/M. wt. of reference = dose of target compound/M. wt. of the target compound.

Table 1. The molecular weight and doses for naproxen, DMSO, and the final Compounds.

Compound sample	Molecular weight	Dose mg/ kg
Naproxen(reference)	230.259	10
DMSO (control)	------	2ml
Gh1	499.44	21.69
Gh2	392.54	17.04
Gh3	471.43	20.47
Gh4	422.56	18.35

Statistical analysis: [54, 55]

The collected data for the present study were analyzed through the Statistical Package for the Social Sciences (SPSS version 26). The data were presented as mean and standard deviation in appropriate tables and graphs. Two-way ANOVA and post hoc analysis were used where appropriate to find out the possible association between the related variables of the current study and to investigate the differences between and within groups. The statistical association was considered significant when the p-value was equal to or less than 0.05 (P-value $\leq$ 0.05).

Results and Discussion

The physical characteristics:

Table (2) offers information on the physical characteristics and identification of intermediates and final chemicals. Through the use of suitable solvent systems, Thin Layer Chromatography (TLC) was used to track the progress of the reaction and evaluate the purity of the products. This analytical technique allowed for the visualization and comparison of the compounds in the reaction mixture.

Table 2. The physical characteristics of both the final compounds and their intermediates.

Comp.	Molecular formula	Molecular weight	Description	%Yield	m.p. ^{o}C	Rf values
1	C15H16O3	244.29	white powder	98	90-92	0.68 A
2	C14H16N2O2	244.29	White fluffy crystals	85	139-141	0.61A
3	C15H15KN2O2S2	358.52	white powder	85	225-228	0.56A
4	C15H14N2OS2	302.41	white powder	88	139-141	0.65A
Gh1	C23H19BrN2O2S2	499.44	Light yellow powder	74	157-160	0.91A
Gh2	C22H20N2OS2	392.54	light gray powder	78	93-96	0.68A
Gh3	C22H19BrN2OS2	471.43	gray powder	73	95-98	0.61A
Gh4	C23H22N2O2S2	422.56	light brown powder	78	117-120	0.73A

Chemistry

Scheme (1) depicts the synthetic procedures that are used to synthesize the ultimate compound targets (Gh1, Gh2, Gh3, and Gh4). In these, the parent nucleus (naproxen) was reacted with methanol in the presence of SOCL2 as a catalyst to create compound (1), naproxen methyl ester. Compound (2), naproxen hydrazide, was generated by refluxing compound (1) with hydrazine hydrate ($NH_2NH_2.H_2O$) while stirring.

The potassium salt of dithiocarbazate (comp. 3). is produced by stirring an ethanolic suspension of compound (2) with CS2 in the presence of KOH.

compound (4), which contains the 1, 3, 4-thiadiazole-2-thiol moiety, must be synthesized via the cyclization technique, which is achieved by stirring a suspension of compound (3) with concentrated H2SO4 at low temperature in an ice path. The target compounds are S-alkylated of compound (4) in the presence of basic ethanol with several alkyl halides (1-4).

FTIR Spectra

The compounds' Fourier transform infrared (FTIR) spectra, which comprised intermediates and end products, showed distinct absorption bands, making it simpler to identify their functional groups. The specific values (v = cm^{-1}) of these characteristic bands are detailed in Table (3).

Table 3.The FTIR Spectra of both the final compounds and their intermediates

Comp.	Bands vibration (cm-1) and their interpretations
1	3005 Aromatic (C-H) stretching
	2974(C-H) asymmetrical stretching of –CH3
	2870(C-H) symmetrical stretching of –CH3
	1732(C=O) stretching of ester
	1600,1504Stretching of (C=C) skeleton
	1442(C-H) in-plane bending of – CH3 group
	1226(C-O-C) stretching of ether
	821 and 794 Out-of-plane bending of β substituted naphthalene
2	3305(N-H) asymmetrical stretching of primary amine
	3278(N-H)symmetrical stretching of primary amine
	3201 (N-H)stretching of secondary amide
	3001 Aromatic (C-H) stretching
	2958 (C-H) asymmetrical stretching of –CH3 group
	2873 (C-H) symmetrical stretching of –CH3 group
	1631 (C=O) stretching of amide
	1604 and 1504 Stretching of (C=C) skeleton
	1261 (C-N) stretching
	1211 (C-O-C) stretching of ether
3	3329 (N-H) stretching of secondary amide
	3132 (N-H) stretching of thioamide
	3055 Aromatic (C-H) stretching
	2981 (C-H) asymmetrical stretching of –CH3 group
	2939 (C-H) symmetrical stretching of –CH3 group
	1631(C=O) stretching of amide
	1604 and 1485 Stretching of (C=C) skeleton
	1265 (C-N) stretching
	1215 (C-O-C) stretching of ether
4	3082(N-H) symmetrical stretching of N of ring
	3062Aromatic (C-H) stretching
	2978(C-H) asymmetrical stretching of –CH3 group
	2877 (C-H) symmetrical stretching of –CH3 group
	2727 (S-H) stretching of thiol thiadiazole ring
	1604 Stretching of (C=N) skeleton
	1064 for (C=S) stretching
	1215 (C-O-C) stretching of ether
Gh1	3028 Aromatic (C-H) stretching
	2974(C-H) asymmetrical stretching of –CH3 group
	2935(C-H) asymmetrical stretching of –CH2 group
	2839 (C-H) symmetrical stretching of –CH3 group
	1693 (C=O) stretching of ketone
	1604 and 1580 Stretching of (C=C) skeleton

	1604 Stretching of (C=N)
	1265 (C-N) stretching
	1230 (C-O-C) stretching of ether
Gh2	3012 Aromatic (C-H) stretching
	2978(C-H) asymmetrical stretching of –CH3 group
	2939(C-H) asymmetrical stretching of –CH2 group
	2881 (C-H) symmetrical stretching of –CH3 group
	2839 (C-H) symmetrical stretching of –CH2 group
	1604 and 1480 Stretching of (C=C) skeleton
	1604 Stretching of (C=N)
	1265 (C-N) stretching
	1230(C-O-C) stretching of ether
Gh3	2978(C-H) asymmetrical stretching of –CH3 group
	2939(C-H) asymmetrical stretching of –CH2 group
	2881 (C-H) symmetrical stretching of –CH3 group
	2839 (C-H) symmetrical stretching of –CH2 group
	1604 Stretching of (C=N)
	1604 and 1543 Stretching of (C=C) skeleton
	1265 (C-N) stretching
	1213 (C-O-C) stretching vibration of ether
Ch4	3046 Aromatic (C-H) stretching
	2978(C-H) asymmetrical stretching of –CH3 group
	2935(C-H) asymmetrical stretching of –CH2 group
	2885 (C-H) symmetrical stretching of –CH3 group
	2839 (C-H) symmetrical stretching of –CH2 group
	1608 Stretching of (C=N)
	1608 and 1546, Stretching of (C=C) skeleton
	1265 (C-N) stretching
	1234(C-O-C) stretching of ether

According to the FTIR spectral data of the synthesized compounds, the Naproxen methyl ester (compound 1) demonstrated ester formation by the appearance of the characteristic sharp band of the (C=O) stretching vibration at 1732 cm^{-1}, which was followed by the disappearance of the characteristic broad band of the (O-H) group of Naproxen's carboxylic acid at 3159 cm^{-1}. The Naproxen hydrazide (compound 2) exhibited the appearance of the characteristic sharp band around 1631 cm^{-1}, indicating the formation of the (C=O) group of the formed hydrazide, followed by the disappearance of the characteristic sharp band of the ester's (C=O) stretching vibration at 1732 cm^{-1}. Two distinct absorption bands were found at 3305 cm^{-1} and 3278 cm^{-1}, attributed to the primary amine N-H hydrazide stretching (Asymmetrical and symmetrical absorption bands).

The potassium salt of dithiocarbazate (comp. 3), exhibited the appearance of 3329cm^{-1} (N-H) stretching vibration of secondary amide, 3132 cm^{-1} (N-H) stretching vibration of thioamide, as well as a distinctive appearance of 1631 cm^{-1} (C=O) stretching vibration of amide.

Later, the disappearance of the peak of the carbonyl group and the appearance of bands at 3082 cm^{-1} of the N-H stretching vibration of the N ring and at 2727 cm^{-1} of the S-H stretching vibration of the thiol thiadiazole ring indicate cyclization. The creation of 1,3,4-thiadiazole-2-thiol revealed two novel bands at 1604 cm^{-1} and 1064 cm^{-1} for (C=N) and (C=S) stretching, respectively, which indicated the formation of 2-mercapto thiadiazole (comp. 4).

At the end of the reaction, the final compounds (Gh1, Gh2, Gh3, and Gh4) were formed, which was indicated by the disappearance of bands of (N-H) stretching vibration of the N of the ring and (S-H) stretching vibration of the thiol thiadiazole ring. This is for all the resulting compounds, and concerning the first compound (Gh1), the appearance of a band at 1693 cm^{-1} of (C=O) of ketone was distinctive.

Generally, the absence of the (C=S) stretching band in the FT-observation IRs confirmed the production of S-alkylated compounds.

^{1}HNMR spectra

The ^{1}HNMR spectra were obtained using a Brucker ultrashield model with a frequency of 300 MHz at Mashhad University of Medical Sciences, where tetramethylsilanes (TMS) were utilized as an internal standard; the chemical shift values were denoted as (δ = ppm). Deuterated dimethylsulfoxide (DMSO-d6) served as the solvent for all the synthesized compounds. The

[1]HNMR spectra exhibited distinct signals that aligned well with the proposed structures of the synthesized compounds. A detailed presentation of the 1HNMR data along with their interpretations can be found in Table (4).

Table 4. The [1]HNMR spectra of the final compounds

Comp.	Chemical Shift,δ= ppm	No. of protons	interpretation
Gh1	1.71	3	d,3H, CH3-
	2.96	3	S,3H, CH3-O
	3.79	2	S,2H, S-CH2 –CO
	4.5	1	q,1H, CH
	6.92-7.84	10	m,10H, aromatic H
Gh2	1.78	3	d, 3H, CH3
	3.88	3	S, 3H, CH3-O
	3.87	2	S,2H, CH2 –S
	4.80	1	q,1H, CH
	7.17-7.84	11	m,11H, aromatic H
Gh3	1.71	3	d, 3H, CH3
	2.68	3	S, 3H, CH3-O
	3.88	2	S, 2H, CH2-S
	4.52	1	q,1H, CH –
	7.07-7.84	10	m,10H, aromatic H
Ch4	1.51	3	d,3H, CH3-
	3.71	3	S,3H, CH3- O
	3.84	3	S,3H, CH3- O
	4.45	2	S,2H, CH2-S
	4.79	1	q,1H, CH
	6.85-7.93	10	m,10H, aromatic H

The [1]HNMR spectra supported the hypothesized derivative structure. Compound (Gh1) exhibited a quartet peak at (4.5) ppm caused by the (C-H) of (CH-CH3), a doublet peak for (CH3) of (CH3-CH) at (1.71) ppm, and a singlet peak at 2.96 ppm caused by esters protons (OCH_3). One singlet peak at 3.79 ppm, generated by (C-H2) protons (S-CH2-C=O), and finally at 6.92–7.84 ppm, multiple peaks belonging to (10H) aromatic.

For the compound (Gh2), [1]HNMR spectra displayed the distinctive signals for a doublet peak for (CH3) of (CH3-CH) at 1.78 ppm, a quartet peak at 4.80 ppm caused by the (C-H) of (CH-CH3), and a singlet peak at 3.88 ppm caused by protons of (OCH_3). One singlet peak at (3.87) ppm, generated by (C-H2) protons (S-CH2-Ring), and finally at (7.17–7.14) ppm, multiple peaks belong to (11H) aromatic.

For the compound (Gh3), [1]HNMR spectra displayed the distinctive signals for a doublet peak for (CH3) of (CH3-CH) at 1.71 ppm, a quartet peak at (4.52) ppm caused by the (C-H) of (CH-CH3), and a singlet peak at (2.68) ppm caused by protons of (OCH_3). One singlet peak at (3.88) ppm, generated by (C-H2) protons (S-CH2-Ring), and finally at (7.07–7.14) ppm, multiple peaks belong to (10H) aromatic.

To sum up, compound (Gh4) showed distinct signals in the [1]HNMR spectra: a quartet peak at (4.79) ppm resulting from the (C-H) bond of (CH-CH3), a doublet peak at (1.51) ppm for (CH3) in (CH3-CH), and a singlet peak at (3.71) ppm attributable to (3) protons from the group of (OCH_3) connected to one benzene ring. And a singlet peak at (3.84) ppm, attributable to (3) protons from the group of (OCH_3) connected to the naphthalene ring. Furthermore, a singlet signal produced by (C-H2) protons (S-CH2-Ring) was detected at (4.54) ppm. At last, many peaks corresponding to (10H) aromatic protons were detected in the 6.85–7.93 ppm range.

The Anti-Inflammatory Activity

For evaluation of the anti-inflammatory activity of the final synthesized compounds (Gh1, Gh2, Gh3, and Gh4), an egg-white-generated paw edema model was used. A subcutaneous injection of undiluted egg whites into the plantar side of the rats' hind paw causes inflammation characterized by plasma extravasations, increased tissue water, plasma protein exudation, and neutrophil extravasations, all of which are caused by arachidonic acid metabolism (50). This in vivo approach offers several benefits over other methods, including quick evaluation by detecting inflammation at the start and over a short time, high paw sensitivity for inflammation, no need for anesthesia, cost-effectiveness, and ease of use. [(56)]

Table 5. Effect of time on the paw swelling thickness among groupings.

Group	Mean ± S.T.D
R	6.856±1.382[a,b,c]
C	7.143±1.384[e]
Gh1	7.186±1.676[a]
Gh2	7.503±1.531[b,e]
Gh3	7.288±1.265[c]
Ch4	7.205±1.396

a There is Significant difference between R, Gh1 (P- value = 0.0162) < 0.05
b There is Significant difference between R, Gh2 (P- value <0.0001) < 0.05
c There is Significant difference between R, Gh3 (P- value <0.0001) < 0.05
e There is Significant difference between C, Gh2 (P- value = 0.0282) < 0.05

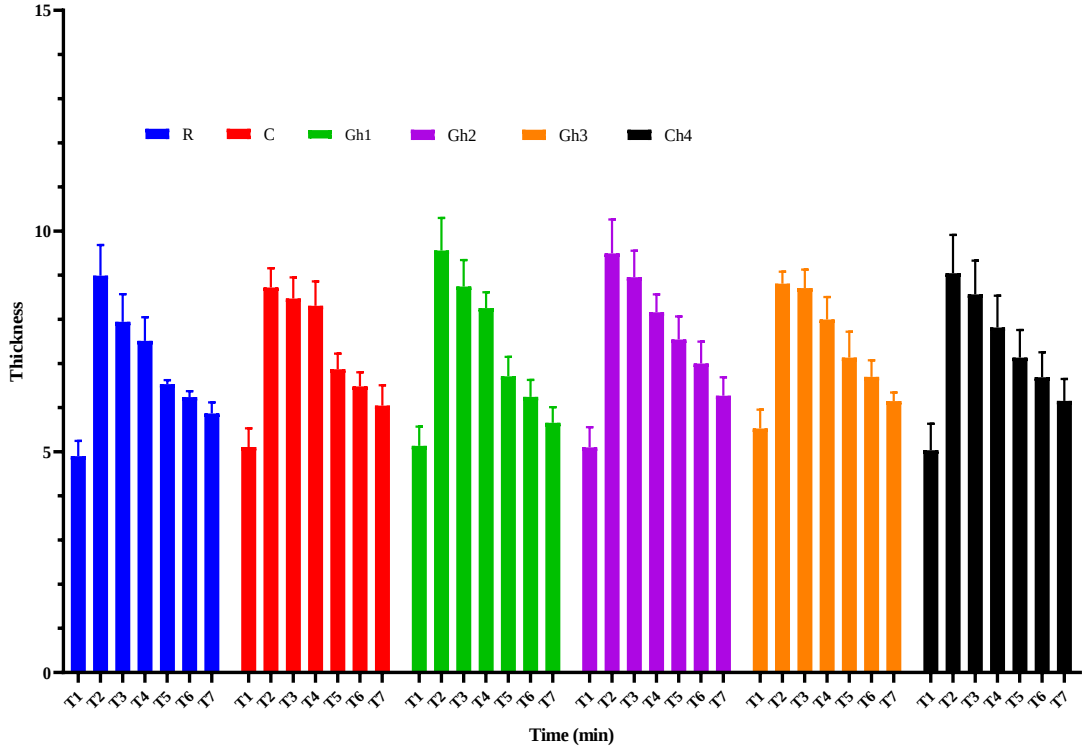


Figure 9. The impact of naproxen, dimethyl sulfoxide (DMSO), and substances Gh1, Gh2, Gh3, and Gh4 on egg whites caused paw edema in rats. The findings are presented as mean ± SEM and percentage

The comparison of the reference drug (naproxen) versus the control (DMSO) and the final compounds (Gh1, Gh2, Gh3, and Gh4), as shown in Table 5, showed the highest percent of inhibition. It was made clear that there were statistically significant differences between these compounds as follows:

1. Reference and compound Gh1 where the P-value was equal to 0.0162 (< 0.05)
2. Reference and compound Gh2 where the P-value was less than 0.0001 (< 0.05)
3. Reference and compound Gh3 where the P-value was less than 0.0001 (< 0.05)
4. Control and compound Gh2, where the P-value was equal to 0.0282 (< 0.05).

It was noted that the effect of each of the manufactured compounds in reducing induced edema was close to the effect of the reference compound, Naproxen, especially the compounds Gh1, Gh2, and Gh3, as shown in Figure (9), the effect of each of the manufactured compounds, the reference compound, and the control in degreasing induced paw edema in rats.

Through an implicit comparison between the different times for each of the compounds investigated, it became clear that the effect of these substances in reducing inflammation increases with time, and these compounds recorded significant statistical values most of the time, which indicates the anti-inflammatory effectiveness that compounds reflect by reducing paw edema.

Conclusion

The aim was to effectively create new variations of naproxen containing 1,3,4-

thiadiazole-2-thiol. Their chemical compositions were identified using ATR-FTIR and ^{1}HNMR spectroscopy. When assessing anti-inflammatory effects in live rats through the egg whites induced paw edema method, it was observed that the development of fresh naproxen derivatives, a nonsteroidal anti-inflammatory drug, retains and sometimes exceeds its anti-inflammatory capabilities. Notably, the compound (Gh1) exhibited enhanced effectiveness at time T7 after 300 minutes of practical application (depicted in figure 9). There exists optimism that these substances, alongside their substantial anti-inflammatory potency, will exhibit few or no adverse effects in contrast to their counterparts, given that the synthetic compounds preserved their anti-inflammatory efficacy even after the modification of the active carbonyl moiety, which is primarily responsible for the majority of the side effects associated with administering naproxen.

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Conflicts of Interest

The work has not received any external funding, and the authors disclose no conflicts of interest.

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Ethics Statements

The scientific and ethical committees of the University of Baghdad's College of Pharmacy approved this work.

Author Contribution

Ghanim, the first author, was responsible for the synthesis of the final compounds, the analysis of IR and H1-NMR data, the discussion of anti-inflammatory medications, the drafting of the text, and the critical revision. The final text of the manuscript was approved by the second author (Zainab) after she reviewed the results.

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تصنيع ، تشخيص وتقييم دوائي اولي لمشتقات النابروكسين الجديدة المحتوية على ١،٣،٤-ثياديازول-٢-ثيول

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الخلاصة

في هذا البحث، تم تركيب مجموعة جديدة من مشتقات ١،٣،٤-ثياديازول-٢-ثيول المستندة على النابروكسين. شملت العملية استرلة مجموعة الكربونيل في النابروكسين باستخدام كلوريد الثايونيل والميثانول، تليها إنشاء هيدرازيد النابروكسين، ثم استخدام CS2 ووسط قلوي لتحويل هيدرازيد النابروكسين إلى ملح البوتاسيوم للدايثيوكاربوزيت. أدت الأكسدة اللاحقة باستخدام حامض الكبريتيك المركز إلى مركب يحتوي على حلقة ثيول ثياديازول. بعد ذلك، تم إنتاج المركبات النهائية : (Gh1، Gh2، Gh3، Gh4)من خلال تفاعل الألكلة. تم التعرف على هذه المركبات باستخدام مطيافية الأشعة تحت الحمراء والرنين المغناطيسي النووي للبروتون. ثم تم تقييم الفعالية المضادة للالتهابات في الجسم الحي عن طريق تحريض التهاب حاد في الفئران المخبرية باستخدام بياض البيض.

تم تصنيع المركبات بنجاح و بمردود مئوي يقترب من ٧٠٪، وتم اكتشاف انها تمتلك فعالية في خفض سمك ودمة المخلب للجرذان المفحوصة ولها تاثير مضاد للالتهابات مشابه لتاثير المادة المرجع (النابروكسين)، بل بعض المركبات فعاليته تفوقت على النابروكسين في بعض أوقات التجربة كما هو الحال في المركب (Gh1) عند الوقت (T7) اي بعد مضي خمس ساعات من التجربة العملية.

الكلمات المفتاحية: مضاد الالتهاب غير الستيرودية، ١،٣،٤-ثياديازول، مركبات حلقية غير متجانسة، النابروكسين،التقييم الدوائي، التخليق، التشخيص .