

Original Article

SYNTHESIS AND PRELIMINARY PHARMACOLOGICAL EVALUATION OF NEW NAPROXEN ANALOGUES HAVING 1, 2, 4-TRIAZOLE-3-THIOL

MONTHER F. MAHDI^a, NOOR H. NASER^{b*}, NETHAL H. HAMMUD^b

^aDepartment of Pharmaceutical Chemistry, College of Pharmacy, Al-Mustansiriya University, Baghdad, Iraq, ^bDepartment of Pharmaceutical Chemistry, College of Pharmacy, Kufa University, Najaf, Iraq
Email: noorh.naser@uokufa.edu.iq

Received: 04 Mar 2017 Revised and Accepted: 19 May 2017

ABSTRACT

Objective: The objective of this search was to synthesize a new naproxen analogues having a 1,2,4-triazole-3-thiol heterocyclic ring, and preliminary pharmacological assessment of the anti-inflammatory activity of the synthesized compounds.

Methods: The synthesis of naproxen analogues that having 1,2,4-triazole-3-thiol heterocyclic ring occur through esterification of naproxen, and then its reaction with hydrazine hydrate, and carbon disulfide, finally different aromatic aldehydes reacted with triazole derivatives of naproxen containing amino group to produce schiff bases.

Results: *In vivo* acute anti-inflammatory activity of the synthesized compounds (Va-Vd) was evaluated in rats using egg-white induced edema model of inflammation in a dose equivalent to (50 mg/kg) of naproxen. All tested compounds were produced a significant reduction in paw edema with respect to the effect of propylene glycol 50% v/v (control group). Compound Vd produced superior anti-inflammatory activity compared to naproxen.

Conclusion: The results obtained in this work give evidence about the valid synthesis of 1,2,4 triazole-3-thiol derivatives of naproxen, which reacted with different aldehydes to yield several schiff bases. The incorporation of benzaldehyde possess para-electron donating group (para-hydroxyl benzaldehyde) will increase the anti-inflammatory activity of naproxen.

Keywords: Naproxen analogues, Synthesis of new naproxen derivatives, Triazole heterocyclic ring

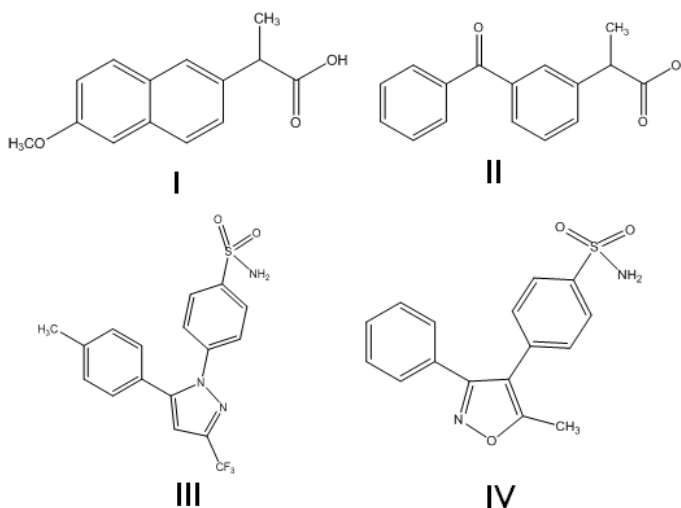
© 2017 The Authors. Published by Innovare Academic Sciences Pvt Ltd. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>)
DOI: <http://dx.doi.org/10.22159/ijpps.2017v9i7.18273>

INTRODUCTION

Non-steroidal anti-inflammatory drugs represent a group of the most widely used medications worldwide [1]. They were used for the treatment of different inflammatory conditions as rheumatoid arthritis, and osteoarthritis, in addition to their analgesic and antipyretic properties [2, 3]. They are acting through competitive inhibition of both cyclo-oxygenase-1 (COX-1) and cyclo-oxygenase-2 (COX-2) enzymes [4, 5]. The first enzyme is constitutive and considered as housekeeping enzyme which responsible for the synthesis of gastric mucosal protective prostaglandins and thromboxane synthesis [6, 7], while the second enzyme was induced

during inflammatory conditions and associated with the synthesis of inflammatory prostaglandins [8]. Therefore; the drugs that inhibit both these enzymes causes a wide range of side effects as bleeding, gastric ulceration and erosion, this will potentiate the direct effect of these medications as they are possess the carboxyl group which responsible for the gastric mucosal damage [9, 10].

This group of non-steroidal called the nonselective drugs e. g. naproxen (I), ketoprofen (II), and diclofenac [11-13]. While the selective agents were those inhibited the COX-2 only, e. g., celecoxib (III) and valdecoxib (IV), by that associated with fewer side effects as gastric ulceration and bleeding [14, 15].



Thus, searching for safer non-steroidal anti-inflammatory drugs was remaining the demand. The researchers focused on either synthesis of selective COX-2 inhibitors or masking the carboxyl group in the chemical structure of the non-steroidal drug, in order to diminish the common side effects as bleeding and gastric irritation that associated with such medications [16].

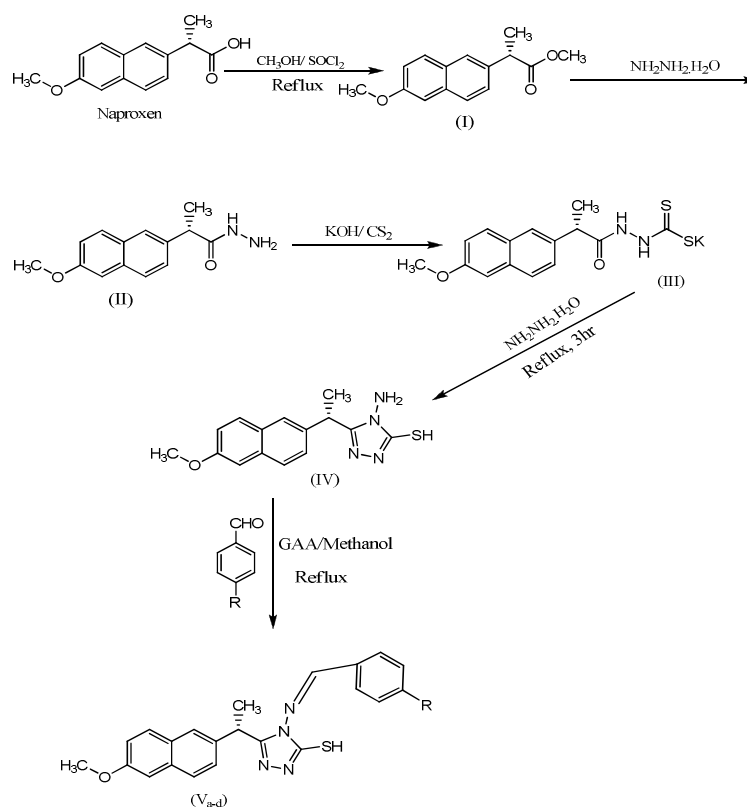
MATERIALS AND METHODS

All reagents and anhydrous solvents were of analytical grade and were supplied from (sigma-aldrich Germany, reidal dehean Germany, and merck, Germany). Melting points were determined by capillary tube method by thomas hover apparatus (England). Retention factor (R_f) values were determined through using ascending thin layer chromatography to ensure the progress of the reaction, and the purity of the synthesized compounds, using two solvent systems; A: toluene: methanol (8:2) [17], and B: chloroform: ethyl acetate (7:3) [18], as mobile phases. Determination of infrared spectra was performed by using fourier transform infrared (FT-IR)

spectrophotometer, elemental microanalysis (CHNOS) were recorded using a euro 3000 elemental analyzer (Italy), and proton nuclear magnetic resonance ($^1\text{H-NMR}$) spectrum was recorded by NMR ultra shield spectrophotometer 500 MHz, bruker avance III (Switzerland).

General procedure

Steps of synthesis of all compounds and their intermediates were presented in scheme 1. The carboxyl group of naproxen were esterified in presence of thionyl chloride in cold methanol. Then naproxen methyl ester was reacted with hydrazine hydrate to give hydrazide, which further reacted with carbon disulfide in presence of potassium hydroxide to yield potassium dithiocarbazine derivative, which undergoes cyclization in presence of hydrazine hydrate to form 1,2,4-triazole-3-thiol heterocyclic ring derivative of naproxen. The primary amine group in the synthesised ring was reacted with different aldehydes to yield series of schiff bases derivatives of naproxen.



Scheme 1: Synthesis of the target compounds and their intermediates

Synthesis of (S) methyl-2-(6-methoxy naphthalene-2-yl) propanoate (I)

Naproxen solution (1g, 4.3 mmol) in absolute methanol (50 ml), was cooled down to $-20\text{ }^\circ\text{C}$, and thionyl chloride (0.31 ml, 4.3 mmol) was added gradually. The mixture was kept at $40\text{ }^\circ\text{C}$ for three hours, then undergo refluxing for additional three hours, and left at room temperature overnight. The methanol was evaporated to dryness, re-dissolved in ethanol and evaporated. This process was repeated several times until removal of thionyl chloride. The residue was recrystallized from ether-methanol [19]. The physical data, R_f values, and percent yield were represented in table 2.

Synthesis of (S)-2-(6-methoxy naphthalen-2-yl) propane hydrazide (II)

A mixture of naproxen methyl ester (I) (2.5 g, 10.8 mmol) and 80% hydrazine hydrate (1.6 ml, 32.5 mmol), was heated under reflux for 15 min., then (10 ml) of absolute ethanol was added from the top of the

condenser to get a clear solution. The mixture was refluxed for 2 h. The alcohol was evaporated and cooled the residue [20]. The crystals of the hydrazide were separated by filtration and recrystallize from ethanol to get beige powder of compound (II). The physical data, R_f values, and percent yield were represented in table 2.

Synthesis of potassium (S)-2-(2-(6-methoxy naphthalen-2-yl) propanoyl) hydrazine carbodithioate (III)

Propanehydrazide (II) (2 g, 8 mmol) was added to a cold solution of potassium hydroxide (0.6 g, 12 mmol), that dissolved in absolute ethanol (250 ml). Then carbon disulfide (0.9 ml, 15 mmol) was added dropwise, and the mixture was stirred continuously at $25\text{ }^\circ\text{C}$ for 12 h. Then the precipitated potassium dithiocarbazine derivative was collected by filtration, washed with anhydrous diethyl ether and dried [21]. The potassium salt was obtained, and used in the next step without further purification. The physical data, R_f values, and percent yield were represented in table 2.

Synthesis of (S)-4-amino-5-(1-(6-methoxynaphthalen-2-yl)ethyl)-4H-1,2,4-triazole-3-thiol (IV)

A suspension of compound (III) (4 g, 11 mmol), hydrazine hydrate 80% (1.1 ml, 22 mmol) and distilled water (20 ml) was refluxed for 3 h. Hydrogen sulfide gas was evolved, the color of the reaction mixture was changed to greenish brown, and a homogenous solution resulted. A deep brown solid was precipitated by addition of cold water (100 ml), then acidify with few drops of HCl (35%) [20]. The product was filtered, washed with cold water (2×50 ml), and re-crystallized from ethanol to form a deep brown powder. The physical data, R_f values, and percent yield were represented in table 2.

Synthesis of Compounds (Va, Vb, Vc, and Vd)

Compound (IV) (1 g, 3.3 mmol) and (3.3 mmol) appropriate aromatic aldehydes [(a-d) listed in table 1], in absolute ethanol (25 ml) were heated under reflux on a water bath for 4 h, during the refluxing period (2-3) drops of glacial acetic acid were added. The solvent was evaporated to a possible extent by a rotary evaporator, and the residue was poured into ice-cooled water to get the product. It was filtered, washed with cold water and dried. The crude product was purified by recrystallization from ethanol [22]. The percent yield, physical data, and R_f values were represented in table 2.

Table 1: Names of aromatic aldehyde's and products number

Aldehyde	Aromatic aldehyde's name	Product number	R group	Quantity
a	benzaldehyde	Va	H	0.34 ml
b	4-bromobenzaldehyde	Vb	Br	0.61 g
c	4-nitrobenzaldehyde	Vc	NO ₂	0.5 g
d	4-hydroxybenzaldehyde	Vd	OH	0.4 g

Spectral analysis

(S)-methyl 2-(6-methoxynaphthalen-2-yl) propanoate (I); IR (cm⁻¹): 3061 (C-H) of aromatic, 1739 (C=O) of ester, and 1332 (C-O) of ester. CHO calculated (C₁₅H₁₆O₃): C, 73.75; H, 6.60; O, 19.65; found: C, 73.70; H, 6.1; O, 19.70; ¹H-NMR (DMSO-d₆) δ (ppm): 7.9-7.1 (m, 6H, Ar-H), 3.8 (s, 3H, CH₃), 3.7 (m, 1H, CH), 3.6 (s, 3H, CH₃), 1.6 (d, 3H, CH₃).

(S)-2-(6-methoxynaphthalen-2-yl) propanehydrazide (II); IR (cm⁻¹): 3,298 and 3,241 (N-H) of NH₂, 3,200 (N-H) of secondary amide, 2,978 and 2,835 (C-H) of alkane, 1,688 (C=O) of secondary amide. CHNO calculated (C₁₄H₁₆N₂O₂): C, 68.83; H, 6.60; N, 11.47; O, 13.10; found: C, 69.02; H, 6.2; N, 11.84; O, 12.8; ¹H-NMR (DMSO-d₆) δ (ppm): 8.0 (s, 1H, NH), 7.9-7.1 (m, 6H, Ar-H), 3.83 (s, 3H, CH₃), 3.5 (m, 1H, CH), 2.0 (s, 2H, NH₂), 1.34 (d, 3H, CH₃).

Potassium (S)-2-(2 (6-methoxy naphthalene-2-yl) propanoyl) hydrazine carbodithioate (III); IR (cm⁻¹): 3,235 (N-H) of secondary amide, 2,976 and 2,832 (C-H) of alkane, 1,690 (C=O) of secondary amide. CHNO calculated (C₁₅H₁₅KN₂O₂S₂): C, 50.25; H, 4.22; N, 7.81; O, 8.93; S, 17.89; found: C, 50.65; H, 4.51; N, 7.24; O, 9.04; S, 17.95; ¹H-NMR (DMSO-d₆) δ (ppm): 13.79 (s, 1H, SH), 7.9-7.1 (m, 6H, Ar-H), 3.83 (s, 3H, CH₃), 3.52 (m, 1H, CH), 2.0 (s, H, NH), 1.34 (d, 3H, CH₃).

(S)-4-amino-5-(1-(6-methoxy naphthalene-2-yl) ethyl)-4H-1,2,4-triazole-3-thiol (IV); IR (cm⁻¹): 3,367 and 3,268 (N-H) of NH₂, 1,554 (C=N) stretching of triazole, 1,353 (C=S) stretching, 1,111 (C-O-O) of ether. CHNOS calculated (C₁₅H₁₆N₄O₃S): C, 59.98; H, 5.37; N, 18.65; O, 5.33; S, 10.67; found: C, 59.95; H, 5.21; N, 18.94; O, 6.0; S, 10.30; ¹H-NMR (DMSO-d₆) δ (ppm): 13.79 (s, 1H, SH), 7.9-7.1 (m, 6H, Ar-H), 5.77 (s, 2H, NH₂), 4.23 (m, 1H, CH), 3.83 (s, 3H, CH₃), 1.68 (d, 3H, CH₃).

(S,Z)-4-(benzylideneamino)-5-(1-(6-methoxynaphthalen-2-yl)ethyl)-4H-1,2,4 triazole-3-thiol (Va); IR (cm⁻¹): 2,974 and 2,891 (C-H) stretching of alkane, 2,740 (S-H) stretching, 1,635 (C=N) stretching of imine, 1,504 (C=N) stretching of triazole, 1,330 (C=S) stretching. CHNOS calculated (C₂₂H₂₀N₄O₃S): C, 68.02; H, 5.19; N, 14.42; O, 4.12; S, 8.25; found: C, 67.85; H, 5.31; N, 14.46; O, 3.98; S, 8.03; ¹H-NMR (DMSO-d₆) δ (ppm): 13.51 (s, 1H, SH), 9.26 (s, 1H, N=CH), 7.9-7.1 (m, 11H, Ar-H), 5.77 (s, 2H, NH₂), 4.23 (m, 1H, CH), 3.83 (s, 3H, CH₃), 1.68 (d, 3H, CH₃).

(S,Z)-4-(4-bromobenzylideneamino)-5-(1-(6-methoxy-naphthalen-2-yl)ethyl)-4H-1,2,4-triazole-3-thiol (Vb); IR (cm⁻¹): 2,970 and 2,886 (C-H) stretching of alkane, 2,746 (S-H) stretching, 1,630 (C=N) stretching of imine, 1,513 (C=N) stretching of triazole, 1,346 (C=S) stretching, 617 (C-Br) stretching. CHNOS calculated (C₂₂H₁₉BrN₄O₃S): C, 56.54; H, 4.10; N, 11.99; O, 3.42; S, 6.86; found: C, 55.92; H, 4.21; N, 12.44; O, 3.68; S, 6.03; ¹H-NMR (DMSO-d₆) δ (ppm): 13.51 (s, 1H, SH), 9.26 (s, 1H, N=CH), 7.9-7.1 (m, 10H, Ar-H), 4.23 (m, 1H, CH), 3.83 (s, 3H, CH₃), 1.68 (d, 3H, CH₃).

(S,Z)-5-(1-(6-methoxynaphthalen-2-yl) ethyl)-4-(4-nitro benzylidene amino)-4H-1,2,4-triazole-3-thiol (Vc); IR (cm⁻¹): 2,971 and 2,888 (C-H) stretching of alkane, 2,742 (S-H) stretching, 1,641 (C=N) stretching of imine, 1,502 (C=N) stretching of triazole, 1,543 (NO₂ asymmetric); 1,356 (NO₂ symmetric), 1,337 (C=S) stretching. CHNOS calculated (C₂₂H₁₉N₅O₃S): C, 60.96; H, 4.42; N, 16.16; O, 11.07; S, 7.40; found: C, 60.95; H, 4.21; N, 16.44; O, 11.45; S, 8.01; ¹H-NMR (DMSO-d₆) δ (ppm): 13.51 (s, 1H, SH), 9.26 (s, 1H, N=CH), 8.33-7.18 (m, 10H, Ar-H), 4.23 (m, 1H, CH), 3.83 (s, 3H, CH₃), 1.68 (d, 3H, CH₃).

(S,Z)-4-((3-mercapto-5-(1(6-methoxy naphthalen-2-yl) ethyl)-4H-1,2,4-triazol-4-ylimino)methyl) phenol (Vd); IR (cm⁻¹): Broad band at 3,456 (O-H) stretching, 2,973 and 2,894 (C-H) stretching of alkane, 2,745 (S-H) stretching, 1,645 (C=N) stretching of imine, 1,504 (C=N) stretching of triazole, 1,331 (C=S) stretching. CHNOS calculated (C₂₂H₂₀N₄O₂S): C, 65.33; H, 4.98; N, 13.85; O, 7.91; S, 7.93; found: C, 65.35; H, 4.29; N, 14.64; O, 8.07; S, 7.84; ¹H-NMR (DMSO-d₆) δ (ppm): 13.51 (s, 1H, SH), 9.26 (s, 1H, N=CH), 7.9-6.85 (m, 10H, Ar-H), 5.35 (s, 1H, OH), 4.23 (m, 1H, CH), 3.83 (s, 3H, CH₃), 1.68 (d, 3H, CH₃).

In vivo anti-inflammatory assessment

The protocol of assessment in this study was approved by the ethical committee of the college of pharmacy/Kufa University (ACE file number 2 at 28-03-2016). *In vivo* anti-inflammatory activity of the synthesized compounds (Va-d) was evaluated using egg-white induced paw edema in rats. The anti-inflammatory activity of the synthesized compounds depends on their ability to decrease the thickness of the rat's paw edema in comparison to standard naproxen treatment.

Protocol of assessment

Albino rats weighing (250±10 g) were supplied from the national center for quality control and drug research and were housed in the special animal house of the college of pharmacy, Kufa University under standardized conditions. Animals were fed with commercial chaw and had access to water *ad libitum* freely. Rats were divided into five groups as in the following:

Group I: Rats were treated with the vehicle (50% v/v propylene glycol), and served as control.

Group II: Rats were treated with naproxen in a dose of 50 mg/kg, suspended in propylene glycol 50%, and served as standard.

Group III-V: Rats were treated with the tested compounds (Va, Vb, Vc, and Vd) in doses 84, 102, 94, 88 mg/kg, respectively (suspended in propylene glycol 50%).

Each group consisting of six rats.

The doses of the tested compounds were determined according to their molecular weights as shown in the following equation [23];

$$\frac{\text{Dose of naproxen (mg)}}{\text{Molecular weight of naproxen (mg/kg)}} = \frac{\text{Dose of the teste compound (mg)}}{\text{Molecular weight of the tested compound (mg/kg)}}$$

Egg-white induced oedema is the model that was used for studying the anti-inflammatory activity of the tested compounds [24]. Acute inflammation was achieved by a subcutaneous injection of undiluted egg-white (0.05 ml) into the planter side of the rat hind paw after 30 minutes of intra-peritoneal administration of the vehicle, standard, or the tested compound. The thickness of the rat's paw was measured by vernea through time intervals (0, 30, 60, 120, 180, 240, and 300 minutes).

Statistical analysis

The data was expressed as mean \pm SEM, they analyzed for their significance by using student t-test (Two-Sample Assuming Equal Variances) for comparison between the values of mean, while comparisons between different groups were made by using ANOVA (one-way analysis using GraphPad prism 7 software). Probability (P) value $<$ 0.05 was considered significant.

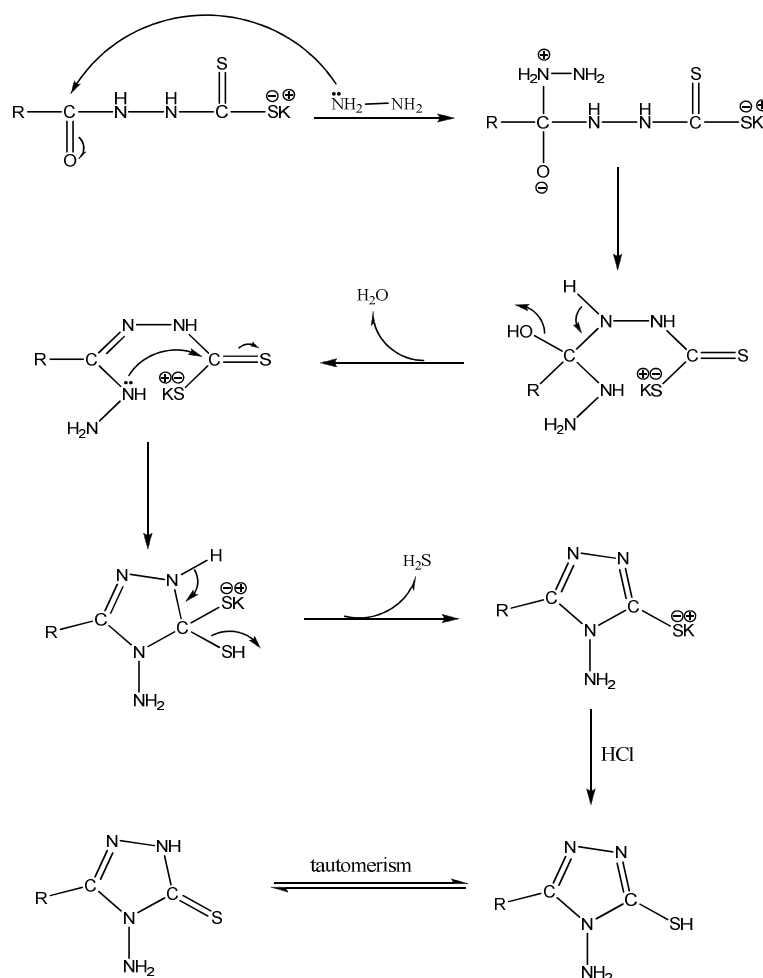
RESULTS AND DISCUSSION

Chemistry

The synthetic procedure led to the synthesis of the final four schiff bases derivatives of naproxen (Va-Vd), and their intermediates (I-IV), was illustrated in scheme 1. Firstly naproxen was esterified by using methanol in presence of thionyl chloride to give acyl chloride intermediate that undergoes reaction with an alcohol to give methyl ester of naproxen. The disappearance of broadband (3219-2939 cm^{-1}), and shifting of C=O stretching from 1728 cm^{-1} to 1739 cm^{-1} indicate the conversion of the carboxyl group in naproxen to its

methyl ester derivative, this was supported by the appearance of singlet signal at 3.68 δ (ppm) for methyl ester group in $^1\text{H-NMR}$ spectrum. The synthesized ester was reacted with hydrazine hydrate to give propane hydrazide in which the amidic C=O stretching band appeared at 1688 cm^{-1} , and the primary amine bands appeared at 3298 and 3241 cm^{-1} , these bands were supported by $^1\text{H-NMR}$ spectrum in which the signal of primary amine appeared at 2 δ (ppm). The reaction is general-base catalysis. Potassium salt of propanoyl hydrazine carbo dithionate was formed by the reaction of the later hydrazide with equimolar of carbon disulfide in basic media of potassium hydroxide. The reaction is nucleophilic addition reaction, in which (NH_2) of compound (II) is the nucleophilic moiety that attacks the carbon of carbon disulfide in basic media [25].

The potassium salt intermediate was cyclized using hydrazine hydrate to give the 1,2,4-triazole-3-thiol derivative of naproxen, this reaction involve several intermediates, the first intermediate nucleophile hydrazine attack of the carbonyl moiety with loss of water molecule, then intramolecular cyclization by neighboring nucleophile amine moiety attack the carbon of carbon disulfide by nucleophile substitution reaction, the potassium salt was formed with concomitant loss of hydrogen sulfide. Acidification of the potassium salt with concentrated hydrochloric acid (35%) liberated compound (IV). There is tautomerism in an equilibrium state between thiol and thione, as shown in scheme 2 [26]. The free amine in the synthesized heterocyclic ring was reacted with different aldehydes (a-d), to yield several schiff bases derivatives of naproxen, this reaction involves nucleophilic substitution, in which the primary amine was attacked the carbonyl carbon in acidic media leading to the formation of imine [27]. The physical characters of the synthesized compounds as melting points and R_f values were listed in table 2.



Scheme 2: Mechanism of synthesis of compound (IV)

Table 2: The characterization and physical parameters of the target compounds and their intermediates

Compound	Molecular formula	Molecular weight	Description	% yield	Melting points (° C)	R _f values
I	C ₁₅ H ₁₆ O ₃	244.29	Yellowish crystals	75.5	88-91	A=0.78
II	C ₁₄ H ₁₆ N ₂ O ₂	244.12	Beige powder	74.3	83-85	A=0.67 B=0.74
III	C ₁₅ H ₁₅ KN ₂ O ₂ S ₂	358.52	Faint brown powder	70.9	188-191	A=0.64 B=0.48
IV	C ₁₅ H ₁₆ N ₄ OS	300.38	Deep brown powder	88	72-73	A=0.76 B=0.86
Va	C ₂₂ H ₂₀ N ₄ OS	388.49	Faint yellow powder	71	62-64	A=0.68 B=0.75
Vb	C ₂₂ H ₁₉ BrN ₄ OS	467.38	Deep yellow crystals	55.7	116-117 d*	A=0.85 B=0.76
Vc	C ₂₂ H ₁₉ N ₅ O ₃ S	433.48	Off white powder	64	103-105	A=0.74 B=0.69
Vd	C ₂₂ H ₂₀ N ₄ O ₂ S	404.48	White powder	52.8	215-218	A=0.79 B=0.78

*decomposition, A: toluene: methanol (8:2), B: chloroform: ethyl acetate (7:3)

Anti-inflammatory activity

Table (3) represents the ability of the synthesized compounds (Va-Vd) to reduce the thickness of the rat's paw edema, that induced by injection of 0.05 ml of egg-white (irritant agent). The anti-inflammatory activity of the synthesized compounds was proportional to their ability to reduce local paw edema [28]. The paw thickness was measured at different time intervals, starting from the time of intraperitoneal injection of vehicle or tested compounds (time zero),

and immediately after injection of the irritant agent (30 min), and after 60, 120, 180, 240, and 300 min. All the tested synthesized compounds were produced a significant reduction in the paw edema when compared them with the control. Compound (Vd) was produced superior anti-inflammatory activity when compared it with the naproxen (standard), due to it reduced the paw edema more effectively than that of naproxen. Compounds Va, Vb, and Vc, show a non-significant reduction in the paw edema when compared with naproxen. These results were illustrated in table 3, and fig. 1.

Table 3: Effect of the synthesized compounds (Va-Vd), propylene glycol (control), and, naproxen (reference), on egg-white induced inflammation of the paw edema in rats

Time (min)	Paw thickness (mm)					
	Post. cont.	STD	Va	Vb	Vc	Vd
0	4.08±0.03	4.1±0.02	4.07±0.06	4.13±0.05	4.05±0.12	4.06±0.15
30	5.74±0.07	5.78±0.05	5.76±0.10	5.78±0.01	5.76±0.04	5.79±0.01
60	5.5±0.12	5.4±0.11 ^a	5.37±0.03 ^a	5.55±0.12 ^b	5.60±0.14 ^b	5.35±0.05 ^a
120	5.31±0.11	5.02±0.06 ^a	5.06±0.05 ^a	5.27±0.04 ^b	5.47±0.06 ^c	4.87±0.12 ^d
180	5.13±0.06	4.62±0.01 ^a	4.66±0.11 ^a	4.59±0.02 ^b	4.67±0.1 ^a	4.48±0.13 ^c
240	4.77±0.08	4.37±0.04 ^a	4.40±0.15 ^a	4.42±0.01 ^a	4.35±0.08 ^a	4.23±0.15 ^b
300	4.54±0.11	4.25±0.01 ^a	4.30±0.13 ^a	4.27±0.11 ^a	4.28±0.12 ^a	4.08±0.03 ^b

Data were expressed as paw thickness (mm) as mean±SEM. The number of animals n=6. ANOVA one-way analysis was used for statistical analysis. Time (0) was represented the time of intraperitoneal injection of the control (propylene glycol), standard (naproxen), and the four tested compounds. Time (30) was represented the time of paw edema induction, which produced by

injection of egg-white. *represents significantly different in comparison to control (p<0.05). (a, b, c, and d) represents non-identical superscripts among different groups were considered significantly different (p<0.05). Post. cont; positive control, STD; naproxen standard treatment, Va-Vd; schiff base derivatives of naproxen.

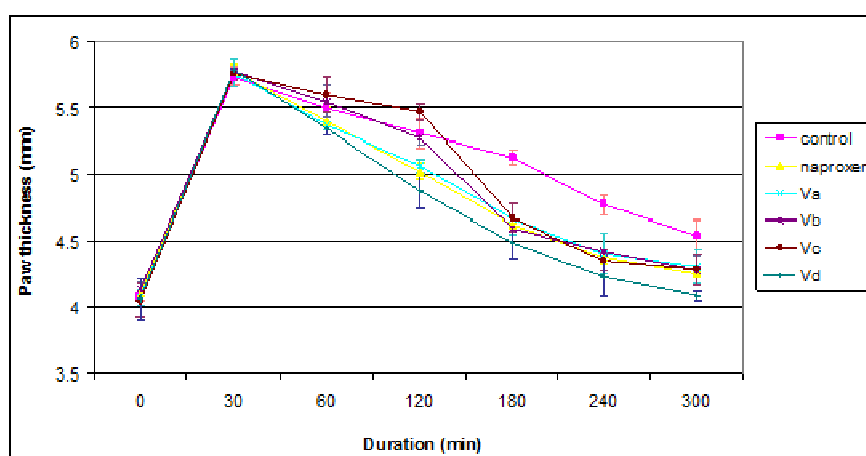


Fig. 1: Percent decrease in rat's paw thickness that induced by egg-white as irritation agent for control, naproxen (STD), and the synthesized compounds (Va-Vd). Data were expressed as paw thickness (mm) as mean±SEM. n=6 for each group. ANOVA one-way analysis was used for statistical analysis

CONCLUSION

In vivo anti-inflammatory assessment was showed the incorporation of the 1,2,4-triazole-3-thiol heterocyclic ring into naproxen molecule was maintained or enhanced the anti-inflammatory activity, depending on the type of aldehyde molecule that form schiff bases with the free amine in the heterocyclic ring. The incorporation of benzaldehyde possess para-electron donating group (para-hydroxyl benzaldehyde), will increase the anti-inflammatory activity of naproxen.

ACKNOWLEDGMENT

The authors are thankful to the staff members in the pharmaceutical chemistry department in the college of pharmacy, Kufa University, for providing facilities for completion the work.

AUTHOR CONTRIBUTION

These authors contributed equally to this work.

CONFLICT OF INTERESTS

All authors have none to declare

REFERENCES

- Mohammed J, Dehghan M, Adil S. Enhancement of dissolution and anti-inflammatory effect of meloxicam using solid dispersions. *Int J Appl Pharm* 2010;2:22-7.
- Prakash PR, Raghavendra Rao HG, Soujanya C. Formulation, evaluation, and anti-inflammatory activity of topical etoricoxib gel. *Asian J Pharm Clin Res* 2010;3:126-9.
- Blanca-Lopez N, Cornejo-Garcia JA, Perez-Alzate D, Perez-Sanchez N, Plaza-Seron MC, Doña I, *et al.* Hypersensitivity reactions to non-steroidal anti-inflammatory drugs in children and adolescents: Selective reactions. *J Investig Allergol Clin Immunol* 2015;25:385-95.
- Ramakrishna S, Mihira V, Raja Vyshnavi K, Ranjith V. Design and evaluation of drug release kinetics of meloxicam sustained release matrix tablets. *Int J Curr Pharm Res* 2012;4:90-9.
- Patel KM, Biswal B, Karna N, Patel J. Preparation and evaluation of sustained release indomethacin tablets using skimmed milk and povidone. *Int J Pharm Res* 2011;3:60-2.
- Datar P, Shendge T. Design, synthesis and stability studies of mutual prodrugs of NSAID's. *Chem Informatics* 2015;1:1-7.
- Nicholas SK, Melissa VC, Anne KZ, Eliana GV, Jing J, Lisa MB, *et al.* Systematic study of constitutive cyclooxygenase-2 expression: Role of NF- κ B and NFAT transcriptional pathways. *PNAS* 2016;113:434-9.
- Rana K, Pandurangan A, Singh N, Tiwari AK. A systemic review of schiff bases as an analgesic, anti-inflammatory. *Int J Curr Pharm Res* 2012;4:5-11.
- Modi CM, Mody SK, Patel HB, Dudhatra GB, Kumar A, Avale M. Toxicopathological overview of analgesic and anti-inflammatory drugs in animals. *J Appl Pharm Sci* 2012;2:149-57.
- Lakshmi PK, Kumar MK, Sridharan A, Bhaskaran. Formulation and evaluation of ibuprofen topical gel: A novel approach for penetration enhancement. *Int J Appl Pharm* 2011;3:25-30.
- Dixit M, Kulkarni PK, Gowtham V, Shivakumar HG. Preparation and characterization of spray dried microparticle and chilled spray dried particle of ketoprofen by spray drying method. *Asian J Pharm Clin Res* 2011;4:138-42.
- Shaheed DQ, Mubarak AK, Libeg AA-A, Abbas HK, AL-Rekabi MD, Husssein AH. Design and synthesis of new derivatives of ketoprofen linked to natural antioxidants (thymol, menthol and guaiaicol) as possible mutual prodrugs. *World J Pharm Res* 2015;4:310-9.
- Reddy PS, Sait S, Hotha KK. Estimation of naproxen related substances in sumatriptan succinate and naproxen sodium tablets by UPLC. *Asian J Chem* 2013;25:9717-21.
- Nissen SE, Yeomans ND, Solomon DH, Lüscher TF, Libby P, Husni E, *et al.* Cardiovascular safety of celecoxib, naproxen, or ibuprofen for arthritis. *N Engl J Med* 2016;1:1-11.
- Zarghi A, Arfaei S. Selective COX-2 inhibitors: a review of their structure-activity relationship. *Iranian J Pharm Res* 2011;10:655-83.
- Abdulhadi SL, Qasir AJ, Abdul Razzak NA. Synthesis of new conjugates of some NSAIDs with sulfonamide as possible mutual prodrugs using tyrosine spacer for colon targeted drug delivery. *Iraqi J Pharm Sci* 2013;22:22-9.
- Mistry BD, Desai KR, Intwala SM. Comparative studies of novel triazole derivative having a chiral center and their antimicrobial activities. *Der Pharma Chem* 2013;5:173-80.
- Sweety D, Iqbal CM, Saravanan J, Mohan S. Synthesis and *in vitro* antimicrobial activity of some novel substituted 1, 3, 4-thiadiazoles. *World J Pharm Res* 2013;2:3199-208.
- Christensen JB. A simple method for synthesis of active esters of isonicotinic and picolinic acids. *Molecules* 2001;6:47-51.
- Jubie S, Sikdar P, Antony S, Kalirajan R, Gowramma B, Gomathy S, *et al.* Synthesis and biological evaluation of some schiff bases of [4-(amino)-5-phenyl-4H-1, 2, 4-triazole-3-thiol]. *Pakis J Pharm Sci* 2011;24:109-12.
- Husain A, Naseer MA, Sarafroz M. Synthesis and anticonvulsant activity of some novel fused heterocyclic 1,2,4-triazolo-[3,4-b]-1,3,4-thiadiazole derivatives. *Acta Poloniae Pharm Drug Res* 2009;66:135-40.
- Zainab Hussain, Emad Yousif, Ahmed Ahmed, Ali Altaie. Synthesis and characterization of schiff's bases of sulfamethoxazole. *Org Med Chem Lett* 2014;4:1.
- Mahdi MF, Rauf A-MR, Kadhim FA-H. Design, synthesis and acute anti-inflammatory evaluation of new non-steroidal anti-inflammatory agents having 4-thiazolidinone pharmacophore. *J Nat Sci Res* 2015;5:21-8.
- Vogel HG, Goethe JH. Drug discovery and evaluation. *Pharmacological assays*. 2nd ed. Springer-Verlag. Berlin Heidelberg; 2002. p. 751.
- Cram DJ, Hammond GS. *Organic synthesis*. 2nd ed. McGraw-Hill Book Company Inc; 1964. p. 561.
- Jamal MY. Synthesis and preliminary antibacterial activity of some new schiff's base compounds derived from 5,5'-dimercapto-4,4'-diamin bis-1,2,4-triazole. *Diala J* 2008;27:71.
- Xavier A, Srividhya N. Synthesis and study of schiff base ligands. *J Appl Chem* 2014;7:6-15.
- Ravi V, Saleem TSM, Patel SS, Raamamurthy J, Gauthaman K. Anti-inflammatory effect of methanolic extract of *Solanum nigrum Linn* berries. *Int J Appl Res Nat Prod* 2009;2:33-6.

How to cite this article

- Monther F Mahdi, Noor H Naser, Nethal H Hammud. Synthesis and preliminary pharmacological evaluation of new naproxen analogues having 1, 2, 4-triazole-3-thiol. *Int J Pharm Pharm Sci* 2017;9(7):66-71.