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Original Article

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

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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 synthesize 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

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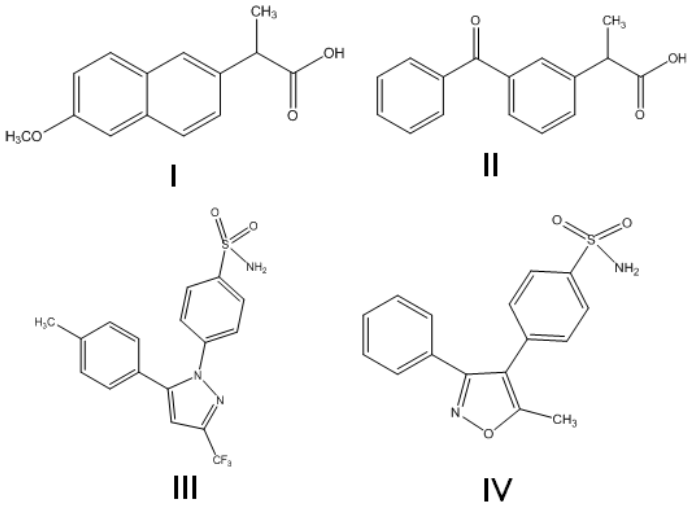
INTRODUCTION

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].



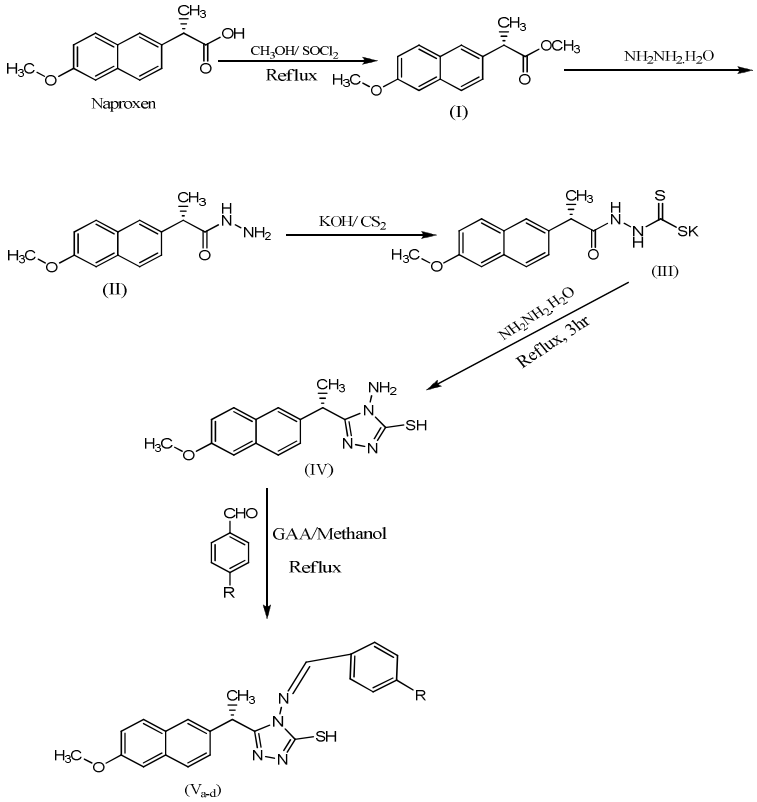
Thus, searching for safer non-steroidal anti-inflammatory drugs was remaining the demand. The researchers focused on either synthesis of selective COX-2 inhibitors or masking the carboxyl group in the chemical structure of the non-steroidal drug, in order to diminish the common side effects as bleeding 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}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 was 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 dithiocarbazinate 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 °C, and thionyl chloride (0.31 ml, 4.3 mmol) was added gradually. The mixture was kept at 40 °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 re-crystallized 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 °C for 12 h. Then the precipitated potassium dithiocarbazinate 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, 1,739 (C=O) of ester, and 1332 (C-O) of ester. CHO calculated ($C_{15}H_{16}O_3$): C, 73.75; H, 6.60; O, 19.65; found: C, 73.70; H, 6.1; O, 19.70; ^{1}H-NMR (DMSO-d6) δ(ppm):7.9-7.1 (m,6H,Ar-H), 3.8 (s,3H,CH_3), 3.7 (m,1H,CH), 3.6 (s,3H,CH_3), 1.6 (d,3H,CH_3).

(S)-2-(6-methoxynaphthalen-2-yl) propanehydrazide (II); IR (cm^{-1}): 3,298 and 3,241 (N-H) of NH_2, 3.200 (N-H) of secondary amide, 2.978 and 2835 (C-H) of alkane, 1,688 (C=O) of secondary amide. CHNO calculated ($C_{14}H_{16}N_2O_2$): 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; ^{1}H-NMR (DMSO-d6) δ (ppm): 8.0 (s,1H,NH), 7.9-7.1 (m,6H,Ar-H), 3.83 (s,3H,CH_3), 3.5 (m,1H, CH), 2.0 (s,2H,NH_2), 1.34 (d,3H,CH_3).

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 ($C_{15}H_{15}KN_2O_2S_2$): 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; ^{1}H-NMR (DMSO-d6) δ (ppm): 8.0 (s,1H,NH amide), 7.9-7.1 (m,6H,Ar-H), 3.83 (s,3H,CH_3), 3.52 (m,1H, CH), 2.0 (s,H,NH), 1.34 (d,3H,CH_3).

(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 NH_2, 1,554 (C=N)stretching of triazole, 1.353 (C=S) stretching, 1,111 (C-O-O) of ether. CHNOS calculated ($C_{15}H_{16}N_4OS$): 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; ^{1}H-NMR (DMSO-d6) δ (ppm): 13.79 (s,1H,SH), 7.9-7.1 (m,6H,Ar-H), 5.77 (s,2H,NH_2), 4.23 (m,1H, CH), 3.83 (s,3H,CH_3), 1.68 (d,3H,CH_3).

(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 ($C_{22}H_{20}N_4OS$): 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; ^{1}H-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,NH_2), 4.23 (m,1H, CH), 3.83 (s,3H,CH_3), 1.68 (d,3H,CH_3).

(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 ($C_{22}H_{19}BrN_4OS$): 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; ^{1}H-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,CH_3), 1.68 (d,3H,CH_3).

(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 (NO_2 asymmetric); 1,356 (NO_2 symmetric), 1,337 (C=S) stretching. CHNOS calculated ($C_{22}H_{19}N_5O_3S$): 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; ^{1}H-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,CH_3), 1.68 (d,3H,CH_3).

(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 ($C_{22}H_{20}N_4O_2S$): 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; ^{1}H-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,CH_3), 1.68 (d,3H,CH_3).

***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 six 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-VI: 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

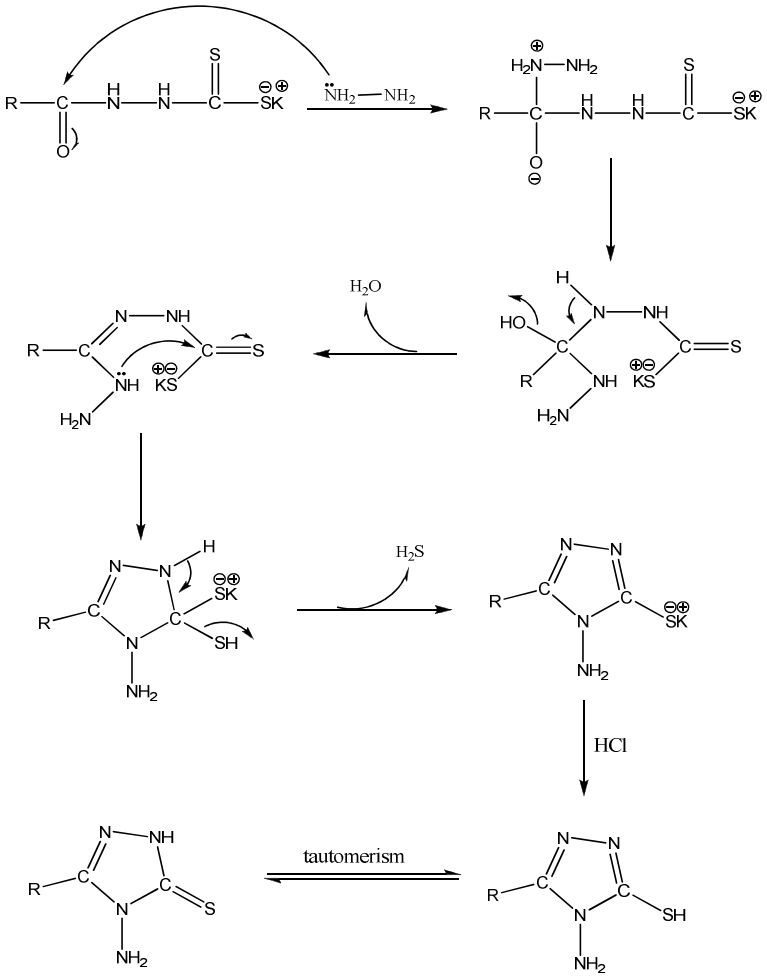
The data was expressed as mean±SEM, they analyzed for their significance by using student t-test (Two-Sample Assuming Equal Variances) for comparison between the values of mean, while comparisons between different groups were made by using ANOVA (one-way analysis using GraphPad prism 7 software). Probability (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}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}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	$C_{14}H_{16}N_2O_2$	244.12	Beige powder	74.3	83-85	A=0.67 B=0.74
III	$C_{15}H_{15}KN_2O_2S_2$	358.52	Faint brown powder	70.9	188-191	A=0.64 B=0.48
IV	$C_{15}H_{16}N_4OS$	300.38	Deep brown powder	88	72-73	A=0.76 B=0.86
Va	$C_{22}H_{20}N_4OS$	388.49	Faint yellow powder	71	62-64	A=0.68 B=0.75
Vb	$C_{22}H_{19}BrN_4OS$	467.38	Deep yellow crystals	55.7	116-117 d*	A=0.85 B=0.76
Vc	$C_{22}H_{19}N_5O_3S$	433.48	Off white powder	64	103-105	A=0.74 B=0.69
Vd	$C_{22}H_{20}N_4O_2S$	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 intra-peritoneal 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.

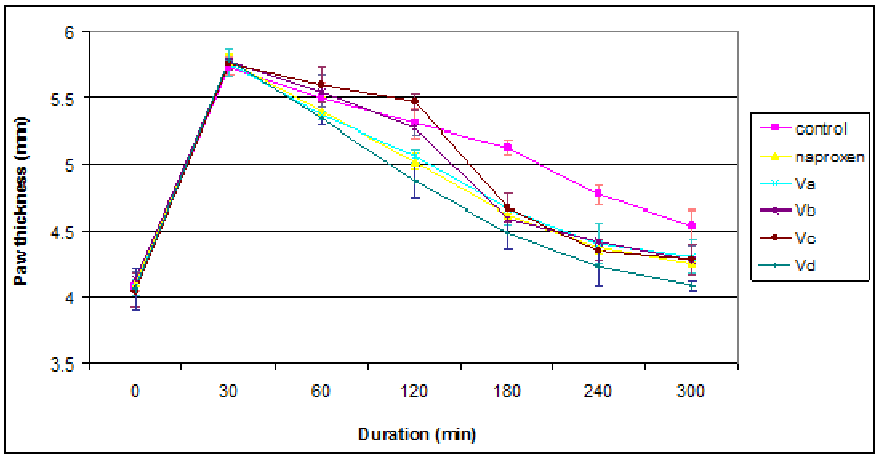


Fig. 1: Percent decrease in rat's paw thickness that induced by egg-white as irritation agent for control, naproxen (STD), and the synthesized compounds (Va-Vd). Data were expressed as paw thickness (mm) as mean±SEM. n=6 for each group. ANOVA one-way analysis was used for statistical analysis

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.

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AUTHOR CONTRIBUTION

These authors contributed equally to this work.

CONFLICT OF INTERESTS

All authors have none to declare

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