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Design, Synthesis and Acute Anti-Inflammatory Evaluation of New Non-Steroidal Anti-Inflammatory Agents Having 4-Thiazolidinone Pharmacophore

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Abstract
Naproxen suffers from general side effects of NSAIDs, owing to the presence of free carboxylic group.
The study was aimed to retard the adverse effects of gastrointestinal origin. New series of 4-thiozolidinones derivatives of naproxen were synthesized $\mathbf{V_{a-f}}$. The structures of synthesized compounds have been established on the basis of their spectral FT-IR and ^{1}H NMR data. *In vivo* acute anti-inflammatory effects of the synthesized compounds were evaluated in rats using egg-white induced edema model of inflammation. The tested compounds and the reference drug produced significant reduction of paw edema with respect to the effect of propylene glycol 50%v/v (control group). Compounds $\mathbf{V_{a-e}}$ exhibited potent anti-inflammatory effect than naproxen (50mg/kg, i.p.) at 180-240 min., while compound $\mathbf{V_f}$ exhibited lower anti-inflammatory effect.
Keywords: Naproxen, 4-Thiazolidinone, Anti-inflammatory activity.

1. Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are used to treat a wide variety of illnesses and diseases, including inflammation, cancers, diabetes (insulin-resistant and related metabolic syndrome); and diseases of the peripheral and central nervous system, e.g., Alzheimer's and Parkinson's (Zhou *et al*.2010; Sobolewski *et al.*2010; Hiroki *et al*.2007; Laura *et al*. 2004*)*. The therapeutic effect of NSAIDs derives from their ability to inhibit PG production. The first enzyme in the PG synthetic pathway is COX. This enzyme converts arachidonic acid AA to the unstable intermediates PGG_2 and PGH_2 and leads to the production of prostanoids, TXA_2, and variety of PGs; these prostanoids have a variety of physiological functions and are also believed to be responsible for causing pain and swelling in inflammatory conditions (Laurence 2011).The three isotypes of COX (COX-1, COX-2 and COX-3) have been identified *(*Chandrasekharan *et al*.2002). COX-1 is a constitutive isoform found in most normal cells and tissues (Seibert *et al.* 1997). It is stimulated by growth factor and hormones and it has been called the housekeeping enzyme (Paloucek *et al.* 2001). The COX-1 plays fundamental roles in the generation of PGs in homoeostasis, and several other physiological functions including gastric protection and control of renal blood flow (Katzung 2013; Claus *et al.*2005).

COX-2 is highly induced in settings of inflammation by cytokines and inflammatory mediators or physiological stress (Lipsky *et al*. 2000). The prostaglandins (PGs) produced by COX-2 play a major role in inflammatory reactions and are responsible for the characteristic inflammatory symptoms (redness, pain, edema, fever and loss of function). The inducible isoform has also been implicated in pathological processes such as various cancer types (colorectal, breast), Alzheimer and Parkinson's diseases (Marnett *et al*. 2002).COX-3 is a recently identified splice variant/isoenzyme of COX-1 and, more suitably, may have been named COX-1b. In humans COX-3 mRNA is found in highest concentrations in the brain and heart (Chen *et al.*2008). The importance of COX-3 is that it could explain the pharmacological actions of paracetamol and other antipyretic/analgesic drugs which are weak inhibitors of COX-1 and COX-2, but penetrate easily into the central nervous system (Regina *et al.* 2005).Selective COX-2 inhibitors differ from traditional NSAIDs in two major ways; Coxibs are less likely to result in NSAID-induced gastropathy, and they do not inhibit platelet function (Bruce 2002). As a result, selective COX-2 inhibitors elicit less clinically significant GI damage and bleeding than conventional NSAIDs (Schnitzer *et al.*2004).

There are numerous biologically active molecules which contain various heteroatoms such as nitrogen, sulphur and oxygen, always drawn the attention of chemist over the years mainly because of their biological importance. Thiazolidinones are thiazolidine derivatives and have an atom of sulfur at position 1, an atom of nitrogen at position 3 and a carbonyl group at position 2, 4, or 5(Verma *et al.*2008).

The 4-thiazolidinone scaffold is very versatile and has featured in a number of clinically used drugs. They have found uses as anti-bacterial, anti-tubercular, anti-inflammatory, anti-convulsant, anti-cancer and anti-viral agents, especially as anti-HIV agents (Handan *et al.*2005; Chen *et al.* 2010; Chandra *et al.* 2009; Srivastava *et al.* 2000; Danylo *et al.*2011; Rawal *et al.*2008). A series of thiazolidine-4-one derivatives from sulfanilamide were evaluated for anti-inflammatory, analgesic and anti-ulcer activity. The compound **(1)** and compound **(2)** with substitution R'-CH_3 showed potential activity (Taranalli *et al.*2009).Compound **(3)**, a thiazolidinone

derivative, which show interesting stereo selective anti-inflammatory/analgesic activities and might preferentially interact with inducible COX-2 isoform (Ottana *et al.* 2002). Absence of 5-arylmethylidene moiety in compound **(4)** enhanced its anti-inflammatory activity and decreased the analgesic activity (Ali *et al.* 2007).as shown in Figure 1. Therefore, a group of 4-thiazolidinone pharmacophore derivatives incorporated in the carboxylate group of a naproxen were designed, synthesized and evaluated as anti-inflammatory agents with expected inhibitory selectivity towards COX-2 enzyme (Flower2003).

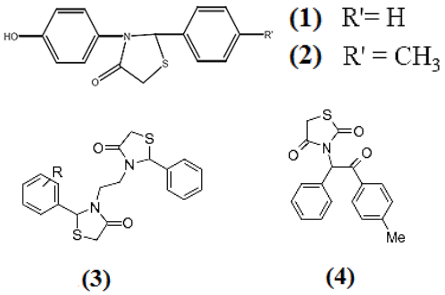


Figure 1. Examples of anti-inflammatory thiazolidinone derivatives

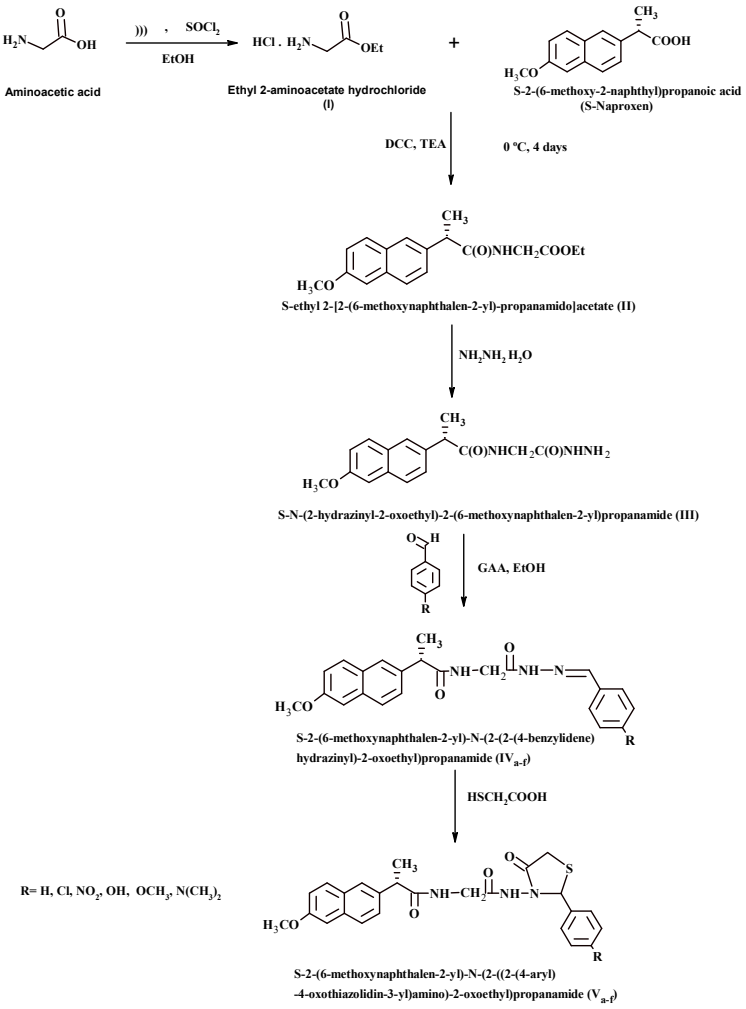
2. Experimental

2.1. General

Electro thermal melting point apparatus and open capillary tubes were used to determine the melting points and are uncorrected. Thin layer chromatography was run on TLC silica gel (60) $F_{254,}$ Merck (Germany), for checking the purity of the products as well as monitoring the progress of the reaction. Chromatograms were eluted by using two different solvent systems: A: Methanol: Acetic acid: Ether: Benzene (02:18:60: 20). B: Chloroform: Methanol (85:15). Compounds were revealed upon irradiation with UV light. IR spectra were recorded on a FTIR, Shimadzu 8100s spectrometer.^{1}HNMR spectra were recorded on Bruker 500 MHz-Avanc III.

2.2 Typical procedure for the reactions

The synthesis of target compounds (**I-V$_{a-f}$**) was achieved following procedures illustrated in Scheme 1.



Scheme 1. Synthesis of the target compounds (I-V_{a-f})

*2.2.1. Synthesis of ethyl 2-aminoacetate hydrochloride (**I**):*

Thionyl chloride (0.8 mL, 11 mmol) was added gradually to absolute ethanol (10 mL), cooled to (0°C). 2-Aminoacetic acid (0.75 g, 10 mmol) was suspended in the reaction mixture and subjected to ultra-sonication at room temperature for (45 min.). On completion of the reaction, the solvent was removed under reduced pressure and the residue was purified by recrystallization from methanol: diethyl ether.

The percent yield, physical data and R_f values are given in Table (2). FTIR: 1748cm^{-1} (C=O ester) and 1250cm^{-1} (C-O-C ester).

*2.2.2. Synthesis of (s)-ethyl-2-[2-(6-methoxynaphthalen-2-yl)-propanamido] acetate (**II**):*

Compound (**I**) (2.8 g, 20 mmol), triethylamine (3 mL, 21 mmol) and Naproxen (4.6 g, 20 mmol) were dissolved in dry DCM (40 mL). The reaction mixture was stirred at (0°C) for (30 min.). To this solution (4.21 g, 20 mmol) DCC in dry DCM (10 mL) was added slowly in a drop wise manner. Reaction mixture was stirred for 3 days at (0°C). Precipitated DCU was filtered off and the solvent was distilled off under reduced pressure. The product obtained was dissolved in ethyl acetate (30mL) and filtered. Ethyl acetate layer was washed with 10% aqueous solution of sodium bicarbonate (3x30mL) and distilled water (3x30mL). Ethyl acetate layer was dried over anhydrous magnesium sulphate and filtered to get a clear solution of product in ethyl acetate. Solvent was evaporated under reduced pressure and the crude product was recrystallized by using hexane: ethyl acetate.

The percent yield, physical data and R_f values are given in Table (2). FTIR: 3293cm^{-1} (NH amid); 1740cm^{-1}(C=O ester) and 1649cm^{-1} (C=O amide). ^{1}H NMR (500 MHz, $CDCl_3$: DMSO-d_6) δ_H: 1.14(3H, t, CH_3 ester); 1.42-1.43 (3H, d, CH_3 naproxen); 3.80-3.84 (3H, m, CH naproxen and CH_2 glycine); 3.87 (3H, s, -OCH_3 naproxen); 4.04-4.08 (2H, q, CH_2 ester); 7.14-7.79 (6H, m, naphthalene CH) and 8.40(1H, br.s, NH amide).

2.2.3. *Synthesis of (s)-N-(2-hydrazinyl-2-oxoethyl)-2-(6-methoxy-naphthalen-2-yl) propanamide (**III**):*

Compound (II) (1 g, 3 mmol) was dissolved in (15 mL) methanol and (0.7 mL, 14mmol) of hydrazine hydrate (90%) was added. The reaction mixture was stirred at r.t. overnight. On the next day the solvent was removed under reduced pressure and the crude product was washed with diethyl ether under stirring to afford the product

in pure state.

The percent yield, physical data and R_f values are given in Table (2). FTIR: 3339 and 3277cm^{-1}($NHNH_2$); 1678cm^{-1} (C=O amidic); 1645cm^{-1} (C=O amide). ^{1}H NMR (500 MHz, $CDCl_3$: DMSO-d_6) δ_H: 4.20 (2H, br.s, NH_2 hydrazide); 8.20 (1H, br.s, NH amide) and 9.01 (1H, s, NH hydrazide) .

*2.2.4. Synthesis of (s)-2-(6-methoxynaphthalen-2-yl)-N-(2-(2-(4-benzylidene) hydrazinyl)-2-oxoethyl) propanamide (**IV$_{a-f}$**):*

Compound (III) (0.3 g, 1 mmol) and (1.1mmol) appropriate aromatic aldehydes (a-f) listed in Table (1) in absolute ethanol (25mL) were heated under reflux on a water bath for 4(hrs.), during the refluxing period (2-3) drops of glacial acetic acid were added. The solvent was distilled off under reduced pressure to a possible extent and 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.

The percent yield, physical data and R_f values are given in Table (2).

*(s)-2-(6-methoxynaphthalen-2-yl)-N-(2-(2-(4-benzylidene) hydrazinyl)-2-oxoethyl) propanamide (**IV$_a$**):*

FTIR: 3291cm^{-1}(NH amide); 1686 cm^{-1} (C=O amidic) and 1643 cm^{-1} (C=O amide & C=N). ^{1}H NMR (500 MHz, $CDCl_3$: DMSO-d_6) δ_H: 8.18 (1H, br.s, NH amide); 8.36 (1H, s, NH -N) and 11.41 (1H, s, NH =CH-Ar).

*(s)-2-(6-methoxynaphthalen-2-yl)-N-(2-(2-(4-chlorobenzylidene) hydrazinyl)-2-oxoethyl)propanamide (**IV$_b$**):*

FTIR: 3293cm^{-1}(NH amide); 1684 cm^{-1} (C=O amidic); 1645 cm^{-1} (C=O amide & C=N) and 1092 cm^{-1} (C-Cl).

*(s)-2-(6-methoxynaphthalen-2-yl)-N-(2-(2-(4-nitrobenzylidene)hydrazinyl)-2-oxoethyl) propanamide (**IV$_c$**):*

FTIR: 3314cm^{-1}(NH amide); 1690 cm^{-1} (C=O amidic); 1643 cm^{-1} (C=O amide & C=N); 1524 cm^{-1} (NO_2 asymmetric); 1343 cm^{-1} (NO_2 symmetric).

*(s)-2-(6-methoxynaphthalen-2-yl)-N-(2-(2-(4-hydroxybenzylidene)hydrazinyl)-2-oxoethyl)propanamide(**IV$_d$**):*

FTIR: 3362cm^{-1}(OH); 3271cm^{-1}(NH amide); 1686 cm^{-1} (C=O amidic) and 1656 cm^{-1} (C=O amide & C=N).

*(s)-2-(6-methoxynaphthalen-2-yl)-N-(2-(2-(4-methoxybenzylidene)hydrazinyl)-2-oxoethyl) propanamide (**IV$_e$**):*

FTIR: 3306cm^{-1}(NH amide); 1682 cm^{-1}(C=O amidic); 1643 cm^{-1} (C=O amide & C=N) and 1254cm^{-1}(OCH_3).

*(s)-2-(6-methoxynaphthalen-2-yl)-N-(2-(2-(4-dimethyaminobenzylidene)hydrazinyl)-2-oxoethyl)propanamide (**IV$_f$**):*

FTIR: 3319cm^{-1}(NH amide); 1680cm^{-1}(C=O amidic); 1643 cm^{-1} (C=O amide & C=N) and 1362cm^{-1}($N(CH_3)_2$).

Table 1. Aromatic aldehyde's name and products no.

No.	Aromatic Aldehyde's name	Product No.	R	Quantity(gm)
a	Benzaldehyde	IV_a	H	0.116
b	4-Chlorobenzaldehyde	IV_b	Cl	0.154
c	4-Nitrobenzaldehyde	IV_c	NO_2	0.166
d	4-Hydroxybenzaldehyde	IV_d	OH	0.134
e	4-methoxybenzaldehyde	IV_e	OCH_3	0.149
f	4-dimethylaminobenzaldehyde	IV_f	$N(CH_3)_2$	0.164

*2.2.5. Synthesis of (s)-2-(6-methoxynaphthalen-2-yl)-N-(2-((2-(4-aryl)-4-oxothiazolidin-3-yl amino)-2-oxoethyl) propanamide (**V$_{a-f}$**) :*

A mixture of Thioglycolic acid (3 mL) and (1 mmol) of either compound (IV_{a-f}) were heated at (60°C) until reaction was complete about (3hrs.). Ethyl acetate (5mL) was added to the reaction mixture; the organic layer was washed with saturated sodium bicarbonate (3x20mL) and water (10mL), dried with anhydrous magnesium sulfate, and concentrated to give oil. The oil washed with diethyl ether to give the final compounds (V_{a-f}). The percent yield, physical data and R_f values are given in Table (2).

*(s)-2-(6-methoxynaphthalen-2-yl)-N-(2-((2-(4-phenyl)-4-oxothiazolidin-3-yl)amino)-2-oxoethyl)propanamide (**V$_a$**):*

FTIR: 3306cm^{-1}(NH amide); 1726cm^{-1}(C=O thiazolidinone); 1680cm^{-1} (C=O amidic) and 1655cm^{-1}(C=O amide); 1215cm^{-1}(C-S). ^{1}H NMR (500 MHz, $CDCl_3$: DMSO-d_6) δ_H: 3.61-3.66 (2H, dd, CH_2 thiazolidinone); 5.76 (1H, s, N-CH -S); 7.14-7.78 (11H, m, naphthalene and aromatic CH); 8.26 (1H, br. s, NH amide) and 10.21 (1H, s, NH -N).

*(s)-2-(6-methoxynaphthalen-2-yl)-N-(2-((2-(4-chlorophenyl)-4-oxothiazolidin-3-yl)amino)-2-oxoethyl) propanamide(**V$_b$**):*

FTIR: 3324cm^{-1}(NH amide); 1728cm^{-1}(C=O thiazolidinone); 1684cm^{-1} (C=O amidic), 1655cm^{-1}(C=O amide); 1213cm^{-1}(C-S); 1088cm^{-1}(C-Cl). ^{1}H NMR (500 MHz, $CDCl_3$: DMSO-d_6) δ_H: 3.67-3.68 (2H, dd, CH_2 thiazolidinone); 5.77 (1H, s, N-CH -S); 7.13-7.79 (10H, m, naphthalene and aromatic CH); 8.24 (1H, br. s, NH amide) 10.20 (1H, s, NH -N).

*(s)-2-(6-methoxynaphthalen-2-yl)-N-(2-((2-(4-nitrophenyl)-4-oxothiazolidin-3-yl)amino)-2-oxoethyl) propanamide(**V$_c$**):*

FTIR: 3277cm^{-1}(NH amide); 1732cm^{-1}(C=O thiazolidinone); 1690cm^{-1} (C=O amidic), 1661cm^{-1}(C=O amide); 1524 cm^{-1} (NO_2 asymmetric); 1346 cm^{-1} (NO_2 symmetric) and 1213cm^{-1}(C-S). ^{1}H NMR (500 MHz, $CDCl_3$:

DMSO-d_6) δ_H: 3.62-3.67 (2H, dd, CH_2 thiazolidinone); 5.92 (1H, s, N-CH -S); 7.13-7.78 (10H, m, naphthalene and aromatic CH); 8.24 (1H, br. s, NH amide) and 10.20 (1H, s, NH -N).

*(s)-2-(6-methoxynaphthalen-2-yl)-N-(2-((2-(4-hydroxyphenyl)-4-oxothiazolidin-3-yl)amino)-2-oxoethyl) propanamide(**V_d**):*

FTIR: 3308cm^{-1}(OH); 3181cm^{-1}(NH amide); 1717cm^{-1}(C=O thiazolidinone); 1697cm^{-1} (C=O amidic), 1649cm^{-1}(C=O amide) and 1211cm^{-1}(C-S). ^{1}H NMR (500 MHz, $CDCl_3$: DMSO-d_6) ^{1}H NMR (500 MHz, $CDCl_3$: DMSO-d_6) δ_H: 3.68-3.71 (2H, dd, CH_2 thiazolidinone); 5.74 (1H, s, N-CH -S); 7.13-7.79 (10H, m, naphthalene and aromatic CH); 8.29 (1H, br.s, NH amide); 9.90 (1H, br.s, OH) and 10.00 (1H, s, NH -N).

*(s)-2-(6-methoxynaphthalen-2-yl)-N-(2-((2-(4-methoxyphenyl)-4-oxothiazolidin-3-yl)amino)-2-oxoethyl) propanamide(**V_e**):*

FTIR: 3310cm^{-1}(NH amide); 1715cm^{-1}(C=O thiazolidinone); 1697cm^{-1} (C=O amidic), 1649cm^{-1}(C=O amide); 1267cm^{-1}(-OCH_3) and 1213cm^{-1}(C-S). ^{1}H NMR (500 MHz, $CDCl_3$: DMSO-d_6) δ_H: 3.68-3.71 (2H, dd, CH_2 thiazolidinone); 5.90 (1H, s, N-CH -S); 7.05-7.79 (10H, m, naphthalene and aromatic CH); 8.28 (1H, br. s, NH amide) and 10.04 (1H, s, NH -N).

*(s)-2-(6-methoxynaphthalen-2-yl)-N-(2-((2-(4-dimethylaminophenyl)-4-oxothiazolidin-3-yl)amino)-2-oxoethyl) propanamide(**V_f**):*

FTIR: 3310cm^{-1}(NH amide); 1720cm^{-1}(C=O thiazolidinone); 1699cm^{-1} (C=O amidic), 1649cm^{-1}(C=O amide); 1390cm^{-1}(N(CH_3)$_2$); 1213cm^{-1}(C-S). ^{1}H NMR (500 MHz, $CDCl_3$: DMSO-d_6) δ_H: 3.65-3.69 (2H, dd, CH_2 thiazolidinone); 5.73 (1H, s, N-CH -S); 6.66 (6H, s, N(CH_3)$_2$); 7.13-7.79 (10H, m, naphthalene and aromatic CH); 8.27 (1H, br.s, NH amide) and 9.50 (1H, s, NH -N).

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

No.	Molecular Formula	Molecular Weight	Description	% yield	Melting point (°C)	R_f
I	$C_4H_{10}NO_2Cl$	139	White crystals	90	145-147	A=0.70 B=0.48
II	$C_{18}H_{21}NO_4$	315	Off white powder	65	84-86	A=0.92 B=0.55
III	$C_{16}H_{19}N_{33}$	301	Yellow powder	78	158-160	A=0.80 B=0.51
Iv_a	$C_{23}H_{23}N_3O_3$	389	white fluffy powder	70	211-213	A=0.65 B=0.70
IV_b	$C_{23}H_{22}N_3O_3Cl$	424	white fluffy powder	71	188-190	A=0.51 B=0.68
IV_c	$C_{23}H_{22}N_4O_5$	434	Yellow fluffy powder	78	180-182	A=0.45 B=0.60
IV_d	$C_{23}H_{23}N_3O_4$	405	White fluffy powder	68	227-229	A=0.28 B=0.42
IV_e	$C_{24}H_{25}N_3O_4$	419	White fluffy powder	74	177-179	A=0.22 B=0.35
IV_f	$C_{25}H_{28}N_4O_3$	432	yellow fluffy powder	69	190-192	A=0.52 B=0.44
V_a	$C_{25}H_{25}N_3O_4S$	463	Off white powder	65	118-120	A=0.76 B=0.62
V_b	$C_{25}H_{24}N_3O_4SCl$	498	Off white powder	62	109-111	A=0.88 B=0.57
V_c	$C_{25}H_{24}N_4O_6S$	508	Yellow powder	68	134-136	A=0.92 B=0.68
V_d	$C_{25}H_{25}N_3O_5S$	479	White powder	61	188-190	A=0.71 B=0.53
V_e	$C_{26}H_{27}N_3O_5S$	493	White powder	63	186-188	A=0.82 B=0.48
V_f	$C_{27}H_{30}N_4O_4S$	506	Yellow powder	65	185-187	A=0.91 B=0.64
Nap.	$C_{14}H_{14}O_3$	230	White powder	-	157-158	A=0.95 B=0.11
Gly.	$C_2H_5NO_2$	75	White powder	-	233-234	A=0.98 B=0.38

3. Preliminary Pharmacological Studies

3.1. Anti-inflammatory Evaluation Study

In vivo acute anti-inflammatory effects of the chemically synthesized compounds (V_{a-f}) were evaluated in egg-white induced paw edema. Their evaluation for their ant-inflammatory activity based on measuring the decreases

of paw thickness.

3.1.1. Methods

A. Animals

Albino rats of either sex weighing (170 ± 10 gm) were supplied by Iraqi center for cancer and medical genetic research and were housed in college of pharmacy- AL-Mustansiriya University under standardized conditions for 10 days for acclimatization. Animals were fed commercial chaw and had free access to water ad *libitum*. Animals were brought to the laboratory, one hour before the experiment, and were divided into eight groups (each group consist of 6 rats) as follows:

Group A: six rats served as control and treated with the vehicle (propylene glycol 50% v/v).

Group B: six rats treated with (s)-naproxen as reference substance in a dose of 50mg/kg dissolved in Propylene glycol.

Group C-H: six rats /group treated with the tested compounds (V_{a-f}) respectively in doses that determined below, also dissolved in propylene glycol.

B. Calculations for Dose Determination

M.Wt. of (s)-Naproxen = 230.26

50mg/kg /230.26 = Dose / M.Wt. of the tested compound.

Table 3. Compounds with their molecular weight and dose

Compounds	Molecular Weight	Dose mg/ kg
(S)-Naproxen	230	50
V_a	463	101
V_b	498	108
V_c	508	110
V_d	479	104
V_e	493	107
V_f	506	110

C. Experimental Design

The anti-inflammatory activity of the tested compounds was studied using the egg-white induced edema model. The paw thickness was measured by vernea at seven time intervals (0, 30, 60, 120, 180, 240, and 300 min) after drug administration. Acute inflammation was produced by a subcutaneous injection of (0.05 ml) of undiluted egg-white into the plantar side of the left hind paw of the rats; 30 min after intra-peritoneal administration of the drugs or their vehicle.

3.1.2. Statistical Analysis

The data was expressed as the mean ± SEM and results were analyzed for statistical significance using student *t*-test (Two Sample Assuming Equal Variances) for comparison between mean values. While comparisons between different groups were made using ANOVA: Two factors without replication. Probability (P) value of less than 0.05 was considered significant.

4.Result and Descussions

The anti-inflammatory activity of the tested compounds has been evaluated in comparison with their vehicle (control group) and naproxen. Table (4) explains the effect of tested compounds (V_{a-f}) in comparison to control and naproxen. The tested compounds and the reference drug produced significant reduction of paw edema with respect to the effect of propylene glycol 50%v/v (control group). All tested compounds significantly limited the inflammation in paw edema, the onset of compound V_d started at time 60 min. while the remaining compounds and naproxen started at 120 min. Compounds V_{a-e} exhibited potent anti-inflammatory effect than naproxen (50mg/kg, i.p.) at 180-240 min., while compound V_f exhibited lower anti-inflammatory effect. However, the effect of all tested compound continued till the end of experiment with statistically significant ($P<0.05$) reduction in paw edema thickness as shown in Figure (2).

4.1. Comparative Analysis

The comparison explains that at 0-30 min. there are no differences among all groups. Compounds (V_{a-e}) at time 120-300 minutes show comparable effect to naproxen; however at interval 180-240 minutes show significantly higher effect. Although; compound V_f significantly limited the increase in paw edema in comparison to control group, but it is significantly lesser effect than naproxen and tested compounds (V_{a-e}) at interval of 120-300 minutes.

Table 4. The anti-inflammatory effect of control, Naproxen and compounds V_{a-f} on egg-white induced paw edema in rats

	compounds	Time (min)						
		0	30	60	120	180	240	300
Paw Thickness (mm) / n=6	Control	4.40±0.08	5.43±0.10	6.18± 0.09	6.96±0.06	7.05±0.10	6.71±0.05	5.39±0.04
	Naproxen	4.36±0.07	5.48±0.08	6.11±0.10	5.71±0.08^{*a}	5.54±0.09^{*a}	5.27±0.10^{*a}	4.73±0.05^{*a}
	V_a	4.37±0.10	5.41±0.05	5.97±0.09	5.66±0.04^{*a}	5.11±0.06^{*b}	4.86±0.05^{*b}	4.52±0.07^{*a}
	V_b	4.40±0.06	5.40±0.10	5.99±0.04	5.68±0.07^{*a}	5.21±0.09^{*b}	4.94±0.05^{*b}	4.61±0.08^{*a}
	V_c	4.38±0.05	5.42±0.04	6.06±0.06	5.73±0.10^{*a}	5.23±0.08^{*b}	4.96±0.09^{*b}	4.55±0.10^{*a}
	V_d	4.35±0.04	5.41±0.10	5.82±0.07*	5.51±0.06^{*a}	5.12±0.05^{*b}	4.88±0.08^{*b}	4.53±0.10^{*a}
	V_e	4.39±0.09	5.40±0.05	6.02±0.06	5.69±0.05^{*a}	5.22±0.07^{*b}	4.93±0.04^{*b}	4.59±0.10^{*a}
	V_f	4.35±0.04	5.39±0.05	5.98±0.07	6.25±0.08^{*b}	5.85±0.10^{*c}	5.57±0.06^{*c}	5.05±0.09^{*b}

Non-identical superscripts (a, b&c) among different tested compounds are considered significantly different ($P<0.05$); *significantly different compared to control ($P<0.05$).Data are expressed in mm paw thickness as mean ± SEM.
n= number of animals. Time (0) is the time of i.p. injection of naproxen and propylene glycol.
Time (30) is the time of injection of egg white (induction of paw edema).

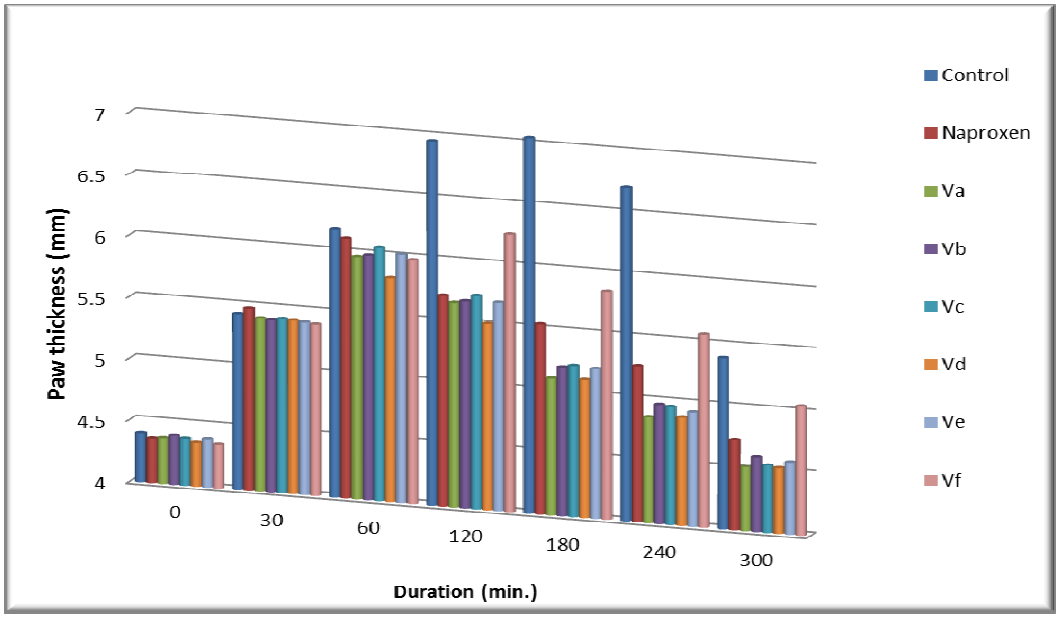


Figure 2. Effect of naproxen, propylene glycol, compounds V_{a-f} on egg-white induced paw edema in rats Results are expressed as mean ± SEM (n = 6 for each group)

5. Conclusions

Acute anti-inflammatory study using egg white induced edema model of inflammation revealed that the incorporation of 4-thiazolidinone pharmacophore into a naproxen maintained or enhanced it is anti-inflammatory activity.

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