Synthesis, characterization and biological evaluation of new potentially active hydrazones of naproxen hydrazide

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ABSTRACT

To synthesize new hydrazone derivatives of naproxen with enhanced anti-inflammatory activity and avoid the ulcerogenic side effects. Hydrazones were synthesized by conjugation of naproxen hydrazide with seven natural and synthetic aldehyde and ketone by using glacial acetic acid as catalyst. The synthesis has been carried out following simple methodology in excellent isolated yields. The structure of the synthesized derivatives has been characterized by elemental microanalysis (CHN), FTIR Spectroscopy, and other physicochemical properties. The anti-inflammatory activity of the synthesized compounds was evaluated in vivo using the egg-white induced edema model in rats, and the results of the biological assay was found to be comparable to Naproxen in this regard. The synthesized hydrazone of naproxen hydrazides with their pronounced anti-inflammatory activity can enhance the anti-inflammatory activity of naproxen to a varying degree according to the type of aldehyde or ketone used.

Keywords: Hydrazones, naproxen, anti-inflammatory activity, aldehyde, ketone.

INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are a group of drugs from diverse structural classes that show analgesic, anti-inflammatory [1], and antipyretic activities [2]. However, the usefulness of these agents is limited due to the higher incidences of the observed gastrointestinal (GI) damage that includes gastric ulceration, perforation and their associated complications [3].

Naproxen sodium, is a nonsteroidal anti-inflammatory drug (NSAID) of the propionic acid class (which puts it in the same class as ibuprofen) and is commonly used for the relief of a wide variety of pain, fever, swelling and stiffness [4,5]. It is the preferred NSAID for long-term use in people with a high risk of cardiovascular complications (such as heart attacks or strokes), due to the fact that it has relatively low risk of causing such complications [6]. Naproxen has an intermediate risk of causing stomach ulcers as compared with ibuprofen, which is low risk, and indomethacin, which is high risk [7].

Hydrazone and acylhydrazone derivatives have been the subject of considerable interest in the development of novel compounds with anti-inflammatory[8-12], antidepressant [13], analgesic [14], anticonvulsant [15], antimicrobial [16], antifungal [17], antitumor [18], antioxidant [19], antimalarial [20], antiplatelet, and antiviral, antimycobacterial and vasodilator activities [21].

Hydrazones are a class of organic compounds that contain the azomethine (\(-\text{NHN=CH}-\)) proton and they are formed by the action of the appropriate substituted hydrazines/hydrazides on aldehydes or ketones by heating in solvents like ethanol, methanol, tetrahydrofuran, butanol, glacial acetic acid, ethanol-glacial acetic acid [22].
The hydrazide-hydrazones derivatives are not only being considered as intermediates but they are also been a very effective organic compounds in their own right. When they are used as intermediates, coupling products can be synthesized by using the active hydrogen component of –CONHN=CH- azomethine group. Hydrazones and acylhydrazones possessing an azomethine –NHN=CH- and O=C-NH-N=CH proton constitute an important class of compounds for new drug development [23].

Carbohydrates and their derivatives have emerged as an important tool for stereoselective synthesis and as a chiral pool for the design of chiral ligands. They are used as chiral building blocks, precursors for drug synthesis and chiral catalysts in asymmetric catalysis despite the importance of carbohydrates in the biological events, but even though the pace of development of carbohydrate based therapeutics have been relatively slow, due to practical synthetic and analytical difficulties [24].

Carbohydrates provide a relatively rigid core with a number of functional (mostly hydroxy) groups in defined spatial orientations. The advantage of carbohydrates is that they provide a series of scaffolds in which all possible isomers either occur naturally or are available by the inversion of individual position [25].

Therefore, the present study was designed to synthesize a hydrazone derivatives of Naproxen with the aim to enhance the anti-inflammatory activity of the final target compounds and being devoid the ulcerogenic side effects.

**MATERIALS AND METHODS**

**Materials and Equipment’s**

Benzyl methyl ketone and Ribose were purchased from Merck (Germany), D-galactose and anhydrous D-glucose were purchased from BDH (England), D-mannose was purchased from Biochemical (England), Glacial acetic acid was purchased from Riedel-de Haén (Germany), Hydrazine hydrate 99.5% was purchased from Alpha medica (India), and 1-naphthaldehyde and Vanillin were purchased from Himedia (India). Naproxen was donated thankfully by The State Company for Drug Industries (SDI, Samara, Iraq).

The quality of all these chemicals together with the other ones used throughout the study and obtained from standard commercial sources were of the highest purity available and used without further purification.

The melting points were determined by the open capillary method using Stuart SMP30 (USA) and were used uncorrected. Cooling of reactions when needed was done using a Julabo chiller VC (F30) (GMBH, Germany). Infra-red spectra were recorded in KBr disc on Shimadzu FTIR 8400 spectrophotometer (Japan), at the College of Pharmacy, University of Baghdad and on Shimadzu FTIR 8400-S spectrophotometer (Japan), at the College of Science, University of Al-Mustansiriyah.

Elemental microanalysis was performed at the College of Pharmacy, University of Karbala using CHN Euro EA Elemental Analyzer (Italy).

The progress of the reaction was monitored by ascending thin layer chromatography which was run on Kieselgel G60 F$_{254}$ pre-coated 0.2 mm thickness Aluminum plates (E. Merck, Germany), and was used as well to check the purity of the product. The synthesized final products and their intermediates were revealed either by derivatization or reactivity toward iodine vapor or by irradiation with UV$_{254}$ light. Chromatograms were eluted by using one or more of the following mobile phases: Solvent system (A): ethyl acetate: n-hexane: methanol (3:2:1 v/v); System (B): acetone: petroleum ether (5:5 v/v); System (C): methanol: ethyl acetate: n-hexane (5:3:2 v/v); and System (D): n-hexane: ethyl acetate: methanol (6:2:2 v/v).

General chemical tests such as the sodium fusion or other specific suitable tests were run to check the presence or absence of certain groups and the purity of the synthesized derivatives and intermediates (Vogel and Shriner). pH measurements of solutions was made using Alkacid™ pH Test Ribbons and Strips purchased from Fisher Scientific (USA).

The biological evaluation of the anti-inflammatory activity of the final target compounds was performed at the Department of Pharmacology and Toxicology, College of Pharmacy, University of Baghdad.

**EXPERIMENTAL SECTION**

The synthetic procedures described below were adapted from those reported earlier in the literature and used with few minor alterations.
A. Chemical synthesis

1. Synthesis of Naproxen Methyl Ester (Intermediate A) [26-28]
An accurately weight amount of Naproxen (10gm, 0.043 mole) was added to 70 ml of absolute methanol contained in a 250 ml round bottom flask, and the mixture was heated with stirring until a clear solution is brought about. Then, the solution was cooled down to ~10 °C and ten milliliters of concentrated sulfuric acid was added drop wise cautiously with continuous stirring, which was accompanied by the appearance of an increasing amount of a white precipitate during the addition process.

Later, it was noticed that towards the completion of the acid addition, the white precipitate cease to form, and the mixture was then set to reflux with stirring at 80 °C for 4 hr. As the temperature of the mixture increases during the refluxing process the precipitate dissolves again and a clear solution reappears. At the end of the 4 hr. reflux period, the solution was cooled down to room temperature, then it was thrown over 250 ml of cold water and later followed by the addition of saturated sodium bicarbonate solution (approximately 10 % w/v) in order to neutralize the excess of the remaining acid present. After each addition of sodium bicarbonate solution the mixture was stirred well with the evolution of CO₂.

As the pH of the mixture increases, a white precipitate of Naproxen methyl ester is produced. When the gas is no longer evolved at the end of the neutralization process, the pH of the solution was checked using Alkacid™ pH Test Strips and if it is less than 8, further portions of saturated sodium bicarbonate solution are to be added. Filter the precipitate (ppt) and wash it with 3 portions of 15 ml cold distilled water, then it was air dried and the product was recrystallized from absolute ethanol to yield intermediate A.

2. Synthesis of Naproxen hydrazide (Intermediate B) [29, 30]
Equimolar amounts of Naproxen methyl ester (Intermediate A) (0.0204 mole, 5 gm) and hydrazine hydrate 99.5% (0.0204 mole, 1 ml) were added to 40 ml of ethanol contained in a 250 ml round bottom flask and the mixture was first stirred overnight at room temperature (RT), after which the it was set to be refluxed at 80 °C for 8 hrs. It was noticed that the suspended mixture will be changed into a clear solution as the temperature increases during the reflux process, while its color changed from colorless to deep yellow with time. At the end of the reflux time, the mixture was left to be stirred overnight at (RT). Later, the formed ppt was filtered off and washed several times with cold distilled water (3 x 15 ml), then the ppt was left to dry and the product was recrystallized from absolute ethanol to afford intermediate B.

3. Synthesis of final Target compounds (Compounds S1-S7) [31, 32]

1) Synthesis of final Target compounds S1-S3
Five drops of glacial acetic acid was added to an ethanolic solution (5 ml) of one of the following aldehydes or ketone [1-naphthaldehyde: S1A (0.00307 mole, 0.416 ml); Vanillin: S2A (0.00307 mole, 0.467 gm); and benzyl methyl ketone: S3A (0.00307 mole, 0.41 ml)] contained in a 100 ml round bottom flask equipped with a magnetic stirrer. Then (0.00307 mole, 0.75 gm) of intermediate B dissolved in 15 ml of absolute ethanol was added with stirring to each of the above mentioned mixtures separately, after which, each reaction mixture was left to stir for (30 min) at RT and it was noticed that the clear mixture has been converted into a suspended one, which wasset to reflux at 80 °C for 8 hrs., and after that it was kept overnight in the freezer. Later, the formed ppt was filtered and recrystallized from the following organic solvents to afford the corresponding intended final target compound: [target compound S1: recrystallized from acetone; S2: from ethanol; and S3: from dichloromethane].

2) Synthesis of final Target compounds S4-S7
Five drops of glacial acetic acid was added to an ethanolic solution (5 ml) of one of the following sugars (which were already dissolved in 1 ml of water) [glucose: S4A; galactose: S5A; and mannose: S6A (0.0041 mole, 0.738 gm); and ribose: S7A (0.0041 mole, 0.615gm)] contained in a 100 ml round bottom flask equipped with a magnetic stirrer. Then (0.0041 mole, 1 gm) of intermediate B dissolved in 15 ml of absolute ethanol was added with stirring to each of the above mentioned mixtures separately, after which the procedure followed the same one mentioned earlier for the synthesis of the target compounds S1-S3, with a slight change in that absolute ethanol was used for the recrystallization process to afford the corresponding intended the final target compounds S4-S7.

The general route illustrated in (Scheme 1) was followed to synthesize the entire intermediate and final target compounds described earlier starting from Naproxen. The physical appearance, percent yield, melting point (m.p. °C) and Rf values of the synthesized compounds together with the elemental microanalysis (CHN Analysis) of the final target compounds (S1-S7) are given in (table 1). The FTIR spectral data (KBr) ν cm⁻¹ of the intermediate and final target compounds are listed below in (table 2).
Scheme 1: Synthetic diagram of the intermediate and final compounds

(S)-2-((6-methoxynaphthalen-2-yl)propanoic acid
Naproxen

1. H₂SO₄ / -10 °C
2. Reflux / 4 hr.

Naproxen methyl ester (Intermediate A)

NH₂NH₂·H₂O

Ethanol / Reflux 8 hrs.

(S)-2-((6-methoxynaphthalen-2-yl)propanoic acid
Naproxen hydrazide (Intermediate B)

Note: For ketones this step ends up with -N=CRR'

Hydrazone
Final target compounds S1-S7

RCHO or RCOR':

SA1: 1-naphthaldehyde
SA2: Vanillin
SA3: Benzyl methyl ketone
SA4: D-Glucose
SA5: D-Galactose
SA6: D-Mannose
SA7: D-Ribose

Scheme 1: Synthetic diagram of the intermediate and final compounds
Group A: Six rats that served as control; and treated with the vehicle (dimethyl sulfoxide) [33].

Group B: Six rats treated with Naproxen as reference substance in a dose of 10mg/kg [34,35], dissolved in dimethyl sulfoxide (DMSO)

Group C–I: Six rats/group treated with the tested compounds S1–S7, respectively, in doses equivalent by weight to 10 mg/kg of Naproxen and dissolved in dimethyl sulfoxide.

The anti-inflammatory activity of the tested compounds was studied using the egg-white induced edema model [36]. Acute inflammation was produced by a subcutaneous injection of undiluted egg-white (0.1 mL) into the plantar side of the left hind paw of the rats; 30 min. after i.p. administration of the drugs or their vehicle. The paw thickness was measured 30 min after injection.

Table 1: Physicochemical characterization data of the synthesized compounds

<table>
<thead>
<tr>
<th>Sym.</th>
<th>Molecular Formula</th>
<th>Molecular Weight</th>
<th>% Yield</th>
<th>Melting point °C</th>
<th>Physical appearance</th>
<th>Rf value</th>
<th>Elemental analysis calculated(found)%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>C   H   N</td>
</tr>
<tr>
<td>A</td>
<td>C₁₀H₁₄NO₃</td>
<td>244</td>
<td>95</td>
<td>87-91</td>
<td>White fluffy powder</td>
<td>(0.9 A  0.83 B)</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>C₂₀H₂₄N₂O₂</td>
<td>244</td>
<td>90</td>
<td>139-141</td>
<td>White crystals</td>
<td>(0.74 A  0.6 D)</td>
<td></td>
</tr>
<tr>
<td>S1</td>
<td>C₂₀H₂₂N₂O₂</td>
<td>382</td>
<td>94</td>
<td>197-201</td>
<td>Off-white crystals</td>
<td>(0.89 A  0.71 B)</td>
<td>78.51 (78.088) 5.80 (5.731) 7.32 (7.524)</td>
</tr>
<tr>
<td>S2</td>
<td>C₂₀H₂₂N₂O₂</td>
<td>378</td>
<td>77.5</td>
<td>204-206</td>
<td>White crystals</td>
<td>(0.73 A  0.51 B)</td>
<td>69.81 (68.657) 5.80 (5.650) 7.40 (7.638)</td>
</tr>
<tr>
<td>S3</td>
<td>C₂₀H₂₂N₂O₂</td>
<td>360</td>
<td>45</td>
<td>180-182</td>
<td>White powder</td>
<td>(0.89 B  0.74 D)</td>
<td>76.64 (75.530) 6.71 (6.615) 7.77 (8.083)</td>
</tr>
<tr>
<td>S4</td>
<td>C₂₀H₂₂N₂O₂</td>
<td>406</td>
<td>30</td>
<td>193-197</td>
<td>White powder</td>
<td>(0.63 A  0.79 C)</td>
<td>59.10 (57.490) 6.45 (6.258) 6.89 (7.132)</td>
</tr>
<tr>
<td>S5</td>
<td>C₂₀H₂₂N₂O₂</td>
<td>406</td>
<td>32</td>
<td>169-171</td>
<td>White powder</td>
<td>(0.64 A  0.82 C)</td>
<td>59.10 (57.159) 6.45 (6.459) 6.89 (7.123)</td>
</tr>
<tr>
<td>S6</td>
<td>C₂₀H₂₂N₂O₂</td>
<td>406</td>
<td>42</td>
<td>155-158</td>
<td>Pale brown powder</td>
<td>(0.52 A  0.75 C)</td>
<td>59.10 (58.070) 6.45 (6.200) 6.89 (6.874)</td>
</tr>
<tr>
<td>S7</td>
<td>C₂₀H₂₂N₂O₂</td>
<td>376</td>
<td>32</td>
<td>97-101</td>
<td>Pale brown powder</td>
<td>(0.3A  0.08 B)</td>
<td>60.63 (60.951) 6.43 (6.568) 7.44 (7.654)</td>
</tr>
</tbody>
</table>

Table 2: IR spectral data of synthesized compounds

<table>
<thead>
<tr>
<th>Sym.</th>
<th>Chemical Name</th>
<th>Characteristics IR spectral bands (KBr) v cm⁻¹ with its Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>(S)-methyl 2-(6-methoxynaphthalen-2-yl)propanoate</td>
<td>3064 aromatic (C-H) stretching, 1732 (C=O) stretching vibration of ester, and 1117 (C-O) stretching vibration of ester.</td>
</tr>
<tr>
<td>B</td>
<td>(S)-2-(6-methoxynaphthalen-2-yl)propanehydrazide</td>
<td>3294 and 3203 (N-H) asymmetric, and sym. stretching vibration secondary amide, 1637 (C=O) stretching of amide I band, and 1599 (N-H) bending vibration of amide II band.</td>
</tr>
<tr>
<td>S1</td>
<td>(S,E)-2-(6-methoxynaphthalen-2-yl-N’-(naphthalen-1-yl)methylene)propanehydrazide</td>
<td>3159 (N-H) stretching vibration of secondary amide, 1654 (C=O) stretching of amide I band, and 1631 (C-N) stretching vibration.</td>
</tr>
<tr>
<td>S2</td>
<td>(S,E)-N’-(4-hydroxy-3-methoxybenzylidene)-2-(6-methoxynaphthalen-2-yl)propanehydrazide</td>
<td>3396 (O-H) stretching vibration, 3188 (N-H) stretching vibration of secondary amide, and 1647 (C=O) stretching of amide I band overlapping with (C=Ne) stretching vibration.</td>
</tr>
<tr>
<td>S3</td>
<td>(S,E)-2-(6-methoxynaphthalen-2-yl)-N’-(1-phenylpropan-2-ylidene)propanehydrazide</td>
<td>3196 (N-H) stretching vibration of secondary amide, 1653 (C=O) stretching of amide I band, and 1631 (C-N) stretching vibration.</td>
</tr>
<tr>
<td>S4</td>
<td>(S,E)-2-(6-methoxynaphthalen-2-yl)-N’-((2S,3R,4R,5R)-2,3,4,5,6-pentahydroxyhexylidene)propanehydrazide</td>
<td>3388-3326 overlapping multiple (O-H) groups stretching vibration with (N-H)stretching vibration of secondary amide, and 1639 (C=O) stretching of amide I band overlapping with (C=Ne) stretching vibration.</td>
</tr>
<tr>
<td>S5</td>
<td>(S,E)-2-(6-methoxynaphthalen-2-yl)-N’-((2S,3R,4S,5R)-2,3,4,5,6-pentahydroxyhexylidene)propanehydrazide</td>
<td>3378-3132 overlapping multiple (O-H) groups stretching vibration with (N-H)stretching vibration of secondary amide, 1646 (C=O) stretching of amide I band, and 1635 (C=Ne) stretching vibration.</td>
</tr>
<tr>
<td>S6</td>
<td>(S,E)-2-(6-methoxynaphthalen-2-yl)-N’-((2R,3R,4R,5R)-2,3,4,5,6-pentahydroxyhexylidene)propanehydrazide</td>
<td>3416-3122 overlapping multiple (O-H) groups stretching vibration with (N-H)stretching vibration of secondary amide, 1649 (C=O) stretching of amide I band overlapping with (C=Ne) stretching vibration.</td>
</tr>
<tr>
<td>S7</td>
<td>(S)-2-(6-methoxynaphthalen-2-yl)-N’-((2S,3S,4R)-2,3,4,5-tetrahydroxypentylidene)propanehydrazide</td>
<td>3485-3174 overlapping multiple (O-H) groups stretching vibration with (N-H)stretching vibration of secondary amide, 1649 (C=O) stretching of amide I band overlapping with (C=Ne) stretching vibration.</td>
</tr>
</tbody>
</table>
measured by vernia at seven time intervals (0, 30, 60, 120, 180, 240, and 300 min) after drug administration. 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.

RESULTS AND DISCUSSION

Many irritant agents have been used in the paw-edema method like dextran, egg-white and carrageenan solution. The paw edema induced by carrageenan has been extensively studied in the assessment of the anti-inflammatory action of steroidal and non-steroidal drugs involving several chemical mediators such as histamine, serotonin, bradykinin and prostaglandins [37]; and it was well documented that the intraplantar injection of egg-white into rat hind paw induces a progressive edema. To assess the validity of the method (paw edema) used for the anti-inflammatory evaluation of newly synthesized compounds, Naproxen was used as a reference compound of known anti-inflammatory activity profile.

(Table 3) shows the effect of Naproxen (reference material) and dimethyl sulfoxide (control) on the egg-white induced paw edema in rats. The differences in paw thickness readings among control and Naproxen groups indicates that the method used in this study (paw edema) is a valid method and can effectively be used for the assessment of the anti-inflammatory effect of the newly synthesized compounds as shown in (fig. 1).

![Fig. 1: The effect of Naproxen (reference), and dimethyl sulfoxide (control) on the egg-white induced paw edema in rats, with Time (30) is the time of egg-white injection.](image)

![Table 3: The effect of Naproxen (reference material) and dimethyl sulfoxide (control) on the egg-white induced paw edema in rats](table)

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Control (n=6)</th>
<th>Naproxen (n=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>3.8±0.03</td>
<td>3.8±0.03</td>
</tr>
<tr>
<td>30</td>
<td>5.8±0.04</td>
<td>5.8±0.04</td>
</tr>
<tr>
<td>60</td>
<td>6.8±0.02</td>
<td>6.1±0.05*</td>
</tr>
<tr>
<td>120</td>
<td>6.5±0.03</td>
<td>5.8±0.02*</td>
</tr>
<tr>
<td>180</td>
<td>6.3±0.03</td>
<td>5.6±0.01*</td>
</tr>
<tr>
<td>240</td>
<td>6±0.05</td>
<td>5.3±0.02*</td>
</tr>
<tr>
<td>300</td>
<td>5.8±0.03</td>
<td>5±0.04*</td>
</tr>
</tbody>
</table>

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 dimethyl sulfoxide (control). Time (30) is the time of injection of egg-white (induction of paw edema).
*Significantly different compared to control (p<0.05).
Table 4 shows the effect of the tested compounds S1-S7 with respect to the control and reference group (Naproxen). All tested compounds effectively limited the increase in paw edema, and the effect of all tested compounds started at 60 minutes (significantly different compared to control). However, the effect of all tested compounds continued till the end of the experiments with statistically significant ($P < 0.05$) reduction in paw edema, as shown in (fig. 2).

### Table 4: The effect of Control, Naproxen and Compounds S1-S7 on egg-white induced paw edema in rats

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Control (n = 6)</th>
<th>Naproxen (n = 6)</th>
<th>S1 (n = 6)</th>
<th>S2 (n = 6)</th>
<th>S3 (n = 6)</th>
<th>S4 (n = 6)</th>
<th>S5 (n = 6)</th>
<th>S6 (n = 6)</th>
<th>S7 (n = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>3.82±0.03</td>
<td>3.84±0.03</td>
<td>3.83±0.02</td>
<td>3.76±0.04</td>
<td>3.79±0.03</td>
<td>3.8±0.04</td>
<td>3.76±0.05</td>
<td>3.74±0.05</td>
<td>3.8±0.03</td>
</tr>
<tr>
<td>30</td>
<td>5.84±0.02</td>
<td>5.82±0.04</td>
<td>5.7±0.03</td>
<td>5.72±0.05</td>
<td>5.79±0.1</td>
<td>5.81±0.01</td>
<td>5.74±0.17</td>
<td>5.63±0.11</td>
<td>5.61±0.11</td>
</tr>
<tr>
<td>60</td>
<td>6.86±0.02</td>
<td>6.14±0.05*a</td>
<td>6.05±0.1*a</td>
<td>6.19±0.07*a</td>
<td>6.06±0.11*a</td>
<td>5.78±0.16*b</td>
<td>6.14±0.16*a</td>
<td>6.15±0.02*a</td>
<td>5.63±0.08*b</td>
</tr>
<tr>
<td>120</td>
<td>6.51±0.03</td>
<td>5.85±0.02*a</td>
<td>5.8±0.12</td>
<td>5.87±0.15*a</td>
<td>5.74±0.11*a</td>
<td>5.61±0.16*a</td>
<td>5.72±0.16*a</td>
<td>5.96±0.04*a</td>
<td>5.39±0.09*b</td>
</tr>
<tr>
<td>180</td>
<td>6.23±0.03</td>
<td>5.64±0.01*a</td>
<td>5.07±0.17*b</td>
<td>5.47±0.2*a</td>
<td>5.38±0.07*a</td>
<td>5.22±0.13*b</td>
<td>5.64±0.08*a</td>
<td>5.61±0.11*a</td>
<td>5.15±0.03*b</td>
</tr>
<tr>
<td>240</td>
<td>6±0.03</td>
<td>5.3±0.02*a</td>
<td>4.7±0.12*a</td>
<td>5.15±0.24*a</td>
<td>5.07±0.05*a</td>
<td>4.88±0.15*b</td>
<td>5.19±0.08*a</td>
<td>5.2±0.17*a</td>
<td>4.8±0.05*b</td>
</tr>
<tr>
<td>300</td>
<td>5.8±0.03</td>
<td>5±0.04*a</td>
<td>4.4±0.11*b</td>
<td>5±0.22*a</td>
<td>4.8±0.09*a</td>
<td>4.53±0.15*b</td>
<td>4.96±0.07*a</td>
<td>5.0±0.04*a</td>
<td>4.4±0.09*b</td>
</tr>
</tbody>
</table>

*Significantly different compared to control ($P < 0.05$).

Non-identical superscripts (a and b) among different groups are considered significantly different ($P < 0.05$).

Data are expressed in mm paw thickness as mean ± SEM. $n = $ number of animals.

**Time (0)** is the time of i.p. injection of tested compounds, Naproxen and dimethyl sulfoxide (control).

**Time (30)** is the time of injection of egg-white (induction of paw edema).

The elemental microanalysis revealed good agreement with the calculated percentages. The percent deviations of the observed/calculated values were found to be within the limits of accurate analysis (table 1).
**CONCLUSION**

The synthesized hydrazone target compounds with their pronounced anti-inflammatory activity may enhance the activity of Naproxen to a different extent depending on the type of aldehyde and ketone used in their synthesis. An *in vivo* anti-inflammatory study showed that the hydrazones has maintained or increased the anti-inflammatory activity compared to their parent compound Naproxen. Compounds **S2, S3, S5, and S6** showed a comparable effect to that of Naproxen, while compounds **S1, S4 and S7** exhibited superior effects to that of Naproxen.

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**REFERENCES**