INTRODUCTION

NSAIDs are one of the most widely used classes of drugs and their consumption is increasing because of their new discovered roles in control of cancer [1,2], cardiac [3] and cerebrovascular [4] neurodegenerative diseases like Alzheimer’s [5]. NSAIDs are mainly used for the management of inflammation and pain in rheumatological conditions like osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, gout and musculoskeletal disorders [6]. All these conditions require long term use of NSAIDs. But one of the serious side effects of NSAIDs on long term use is gastrointestinal toxicity, the free carboxylic group (–COOH) was temporarily masked by esterification with alcoholic/phenolic –OH of natural antioxidants thymol, guaiacol, menthol and vanillin. In order to obtain the derivatives with improved in vivo lability, the double ester prodrugs i.e. ketoprofen-antioxidant through the glycolic acid spacer (-CH₂COO-) have been synthesized. These mutual prodrugs were evaluated for their anti-inflammatory, analgesic and antiulcer properties. The results indicate that there is merit to extend the therapeutic utility of this potential NSAID by developing the ketoprofen-antioxidant mutual prodrugs as gastroprotective NSAIDs.

Keywords: NSAIDs, Gastric ulcer, Prodrug, Anti-inflammatory, Analgesic, Antiulcer.

Synthesis and Evaluation of Prodrugs of Ketoprofen with Antioxidants as Gastroprotective NSAIDs

SHIKHA SEHAJPAL1,2, DEO NANDAN PRASAD3 and RAJESH K. SINGH3,*

1Gujranwala Guru Nanak Khalsa College of Pharmacy, Civil Lines, Ludhiana-141 001, India
2Faculty of Pharmacy, I.K. Gujral Punjab Technical University, Jalandhar-144603, India
3Department of Pharmaceutical Chemistry, Shivalik College of Pharmacy, Nangal-140 126, India

*Corresponding author: E-mail: rksingh244@gmail.com

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Ketoprofen-antioxidant mutual prodrugs were synthesized to reduce the gastrointestinal effects associated with ketoprofen. For reducing the gastrointestinal toxicity, the free carboxylic group (–COOH) was temporarily masked by esterification with alcoholic/phenolic –OH of natural antioxidants thymol, guaiacol, menthol and vanillin. In order to obtain the derivatives with improved in vivo lability, the double ester prodrugs i.e. ketoprofen-antioxidant through the glycolic acid spacer (-CH₂COO-) have been synthesized. These mutual prodrugs were evaluated for their anti-inflammatory, analgesic and antiulcer properties. The results indicate that there is merit to extend the therapeutic utility of this potential NSAID by developing the ketoprofen-antioxidant mutual prodrugs as gastroprotective NSAIDs.

Keywords: NSAIDs, Gastric ulcer, Prodrug, Anti-inflammatory, Analgesic, Antiulcer.

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phytophenols and alcohol so as to get both the anti-inflammatory action of parent NSAID as well as the antioxidant effect of phytophenols/alcohol. For this ester prodrugs of ketoprofen with various natural antioxidants like thymol, guaiacol, menthol, vanillin were synthesized. These natural phytophenols/alcohol have shown not only the antioxidant properties, but also antimutagenic, anticarcinogenic, anti-inflammatory properties [14,15]. Thus ketoprofen-phytophenols/alcohol mutual prodrugs were prepared with the objective to get not only the complementary/additional [16,17] and synergistic pharmacological actions [18], but also the reduced gastrointestinal side effects. These naturally occurring compounds have been traditionally in use as a food additive and have well documented safety profile [19]. Other examples of mutual prodrugs with natural antioxidant have been reported for diclofenac [20], ibuprofen [21], aceclofenac [22] and mefenamic acid [23,24].

Sometimes simple aliphatic/aromatic esters may not be sufficiently labile in vivo so as to ensure sufficiently high rate and extent of release of parent drug from the prodrug. This can be achieved by following double ester prodrug approach in which the terminal ester group is sterically less hindered [25]. Thus, in the present study ketoprofen-phytophenols/alcohol ester prodrugs were synthesized through the OCH2COO- (glycolic acid spacer) linkage. All the prepared prodrugs were evaluated for their anti-inflammatory, analgesic and antiulcer and antioxidant properties. They were also evaluated for their solubility (phosphate buffer pH 7.4) and for octanol-water partition coefficient. These NSAIDs-antioxidant prodrugs are expected to be absorbed in an inactive form, through the gastrointestinal tract and cleaved to release the parent NSAID and the antioxidant (phytophenols/alcohols), which may prevent the NSAID induced gastric ulceration through their carboxyl masking effect and through the antioxidant properties by quenching ROS.

**EXPERIMENTAL**

The melting points were determined on Veego-programmable melting point apparatus (microprocessor based) and are uncorrected. \(^1\)H NMR and \(^13\)C NMR spectra were obtained using Bruker AC-400 F, 400 MHz spectrometer and are reported in parts per million (ppm), downfield from tetramethylsilane (TMS) as internal standard. Infrared spectra were obtained with Perkin Elmer 882 Spectrum and RXI, FT-IR model. Elemental analyses were carried out on a Perkin-Elmer 2400 CHNS/O elemental analyzer. Reactions were monitored and the homogeneity of the products was checked by TLC, which were prepared with silica gel G and activated at 110 °C for 30 min. All the solvents were dried and freshly distilled prior to use, according to standard procedure.

**Preparation of ketoprofen-antioxidants ester prodrugs with spacer:** The general method for the preparation of mutual prodrugs of ketoprofen and phytophenols/alcohols with the spacer, in a first step the synthesis of the required chloroacetyl derivative of phytophenols/alcohols was done [26]. The respective chloroacetyl derivatives were obtained in good yield. They were identified through TLC and by comparing their IR spectral data with literature reports. In second step, the respective chloroacetyl derivatives were condensed with ketoprofen.

The sequence of steps involved in the preparation of these compounds is shown in Fig. 1. The general chemical structure of the synthesized mutual prodrugs of ketoprofen (I) with various phytophenols/alcohol, through glycolic acid spacer (-OCH2COO-) is (II-V) shown in Fig. 1, where the respective Ar/R are as shown in Table-1.

![Fig. 1. Sequence of steps for the synthesis of ketoprofen-OCH2COO-phytophenol/alcohol mutual prodrugs](image)

**Step-I:** The reaction was performed at 0 °C using antioxidant(phytophenols/alcohols) (10 mmol), chloroacetyl chloride (10 mmol = 0.795 mL) and triethylamine (TEA) (10 mmol = 0.696 mL) in dry chloroform (20 mL) as the solvent for 1.5 h followed by 5 h stirring at room temperature to obtain chloroacetyl derivative of antioxidant. To the reaction mixture, add ice cold water and extracted with ethyl acetate. The ethyl acetate layer was shaken with 1 M sodium carbonate solution for 15 min (3 × 25 mL), distilled water (3 × 25 mL), 0.05 N HCl (3 × 25 mL), distilled water (3 × 25 mL) and finally with (25 mL) brine solution (saturated NaCl solution). The ethyl acetate extract was dried over anhydrous sodium sulfate and recrystallized from ethanol to get compounds (a-d).

**Step-II:** Chloroacetyl derivatives of antioxidant (a-d) were mixed with sodium iodide NaI (10 mmol = 0.749 g) in DMF as a solvent at 0 °C followed by 5 drops of triethylamine and pinch of DMAP. Ketoprofen (10 mmol = 2.54 g) was added in the mixture under 0 °C and allowed to stir overnight at room temperature. To the reaction mixture, add ice cold water and ethyl acetate. The ethyl acetate layer was shaken with 1 M sodium carbonate solution for 15 min, distilled water (3 × 25 mL), 0.05 N HCl (3 × 25 mL) and finally with (25 mL) brine solution (saturated NaCl solution). The ethyl acetate extract was dried over anhydrous sodium sulfate. Purification was done by column chromatography using silica gel (60-120 mesh size) and a mobile phase with gradient elution of ethyl acetate in n-hexane up to 6 %. The prodrugs (II-V) were obtained in reasonably good yields (Table-1).

**Chemical characterization of synthesized prodrugs-antioxidant prodrugs with glycolic spacer (II-V)**

2-(2-Isopropyl-5-methylphenoxy)-2-oxoethyl-2-(3-benzyloxyphenyl)propanoate (II): IR (KBr, \(\nu_{max}, \text{cm}^{-1}\)): 3460.26 (aromatic C-H st), 2985.42 (aliphatic C-H str.) 1235.24, 1457.31 (aromatic C-O ester), 1735.53 (C=O str.), 1648.93 (C=O str. ketone), 1457.31 (aromatic C=C str.), 781-7.79 (3H, m, aromatic H), 7.6 (dt, 1H, aromatic H), 7.60-
TABLE-I

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Compounds</th>
<th>ArO-RO-</th>
<th>R∞ value</th>
<th>Yield (%)</th>
<th>Solubility (µg/mL)</th>
<th>log P</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Standard (ketoprofen [I])</td>
<td>H</td>
<td>0.50</td>
<td>–</td>
<td>0.5</td>
<td>3.21</td>
</tr>
<tr>
<td>II</td>
<td>K.T.S (ketoprofen-OCH2COO-thymol prodrug) II</td>
<td>H</td>
<td>0.63*</td>
<td>56.4</td>
<td>5.06</td>
<td>6.09</td>
</tr>
<tr>
<td>III</td>
<td>K.G.S. (ketoprofen-OCH2COO-Guaiacol prodrug) III</td>
<td>H</td>
<td>0.54*</td>
<td>48.3</td>
<td>10.37</td>
<td>4.23</td>
</tr>
<tr>
<td>IV</td>
<td>K.M.S. (ketoprofen-OCH2COO-menthol prodrug) IV</td>
<td>H</td>
<td>0.79**</td>
<td>42.6</td>
<td>7.81</td>
<td>5.76</td>
</tr>
<tr>
<td>V</td>
<td>K.V.S (ketoprofen-OCH2COO-vanillin prodrug) V</td>
<td>H</td>
<td>0.72**</td>
<td>52.5</td>
<td>12.52</td>
<td>4.21</td>
</tr>
</tbody>
</table>

Mobile phase: *10 % ethyl acetate in n-hexane, **5 % methanol in chloroform

6.09 (2H, m, aromatic H) 7.49-7.41 (3H, m, aromatic H) 6.66-6.64 (3H, m, aromatic H thymol), 1.29-1.27 (6H, d, CH(CH3)2 thymol), 1.55-1.53 (3H, s, CH-CH3), 2.30 (3H, s, Ar-CH3), 2.95-2.90 (1H, m, CH (CH3)2 thymol), 3.86-3.79 (1H, q, CH(CH3)2), 4.90-4.73 (2H, s, O-CH2COO). 13C NMR (CDCl3): 20.6 (Ar-CH2), 22.8 (CH2), 26.8 (CH=CH2 thymol), 60.7 (O-CH2-COO), 121.79-136.49 (Ar-Cs), 167.0 (CH=O=C=O), 176.14 (CH=CH=O), 196.97 (Ar=OAr). Anal. Calcd. (Found) % for C28H22O6: C, 71.76 (71.55); H, 5.30 (5.47); O, 22.54 (21.89).

II

1H NMR (CDCl3): 7.81-7.74 (3H, m, aromatic H), 6.96-6.89 (2H, m, aromatic H guaiacol), 7.18-7.11 (2H, d, aromatic-H guaiacol), 4.90-4.73 (2H, s, O-CH2COO), 12.17 (O-CH2-COO), 3.86-3.78 (1H, q, CH-CH3), 3.83 (3H, s, Ar-CH3). 13C NMR (CDCl3): 10.53 (CH=CH2 COO), 45.29 (Ar-CH2 & CH2), 52.20 (Ar-OCH2), 61.47 (O-CH2-COO), 128.32-141.03 (aromatic-Cs), 150.9 (Ar-C-OCH2 & CH=CH2), 140.2 (HC=O (OCH2)), 177.59 (CH=O (OAr)), 196.7 (Ar-OC=OAr). Anal. Calcd. (Found) % for C28H22O6: C, 71.76 (71.55); H, 5.30 (5.47); O, 22.54 (21.89).

V

13C NMR (CDCl3): 16.42 (CH-CH2 menthol), 18.45 (CH3 ketoprofen), 21.09-22.10 (CH (CH3)2 menthol), 23.12 (CH2 menthol), 26.63 (CH (CH3)2 menthol), 47.04 (CH menthol), 34.67 (CH3 menthol), 71.78 (O=CH menthol), 173.8 (Ar=OAr), 128.56-141.74 (Ar-Cs), 167.2 (O-CH2=C=O), 45.22 (CH=CH ketopron). Anal. Calcd. (Found) % for C28H34O5: C, 74.64 (74.49); H, 7.61 (7.79); O, 17.85 (17.12).

Physico-chemical evaluation: One main aim of synthesizing these prodrugs is that they should have optimum solubility and lipophilicity required for bioavailability. These physico-chemical properties of drug molecules have been used to predict passive absorption in vivo [31]. Hence the octanol-water partition coefficient P and log P is used for the measurement of lipophilicity of the drug molecule. Higher the partition coefficient, the greater is the lipophilicity and more is the absorption. The drugs having a partition coefficient of 100 or more (i.e. log P ≥ 2) and the solubility of 10 µg/mL are considered fit for effective bioavailability after oral administration. Partition coefficient was calculated as:

Partition coefficient (P) = \frac{Conc. of drug in octanol}{Conc. of drug in buffer} \times Dilution factor
In the present study, the solubility study for ketoprofen and its prodrugs (ketoprofen-OCH2COO-phytophenols/alcohol) has been done in phosphate buffer (pH 7.4). The data for partition coefficient and solubility studies for ketoprofen-OCH2COO-phytophenols/alcohol is given in Table-1. The physico-chemical properties like partition coefficient and solubility influence the therapeutic activity and pharmacokinetic profile of drugs. If the agent has limited solubility (≤ 1%) in gastrointestinal fluids, then it shows poor gastrointestinal absorption. Ketoprofen has limited solubility so its esters were prepared and they were found to have fair solubility in phosphate buffer (pH = 7.4) and greater lipophilicity than ketoprofen. Thus prepared ketoprofen prodrugs are suitable for oral administration.

**Biological evaluation/pharmacological studies:** Since the ketoprofen-antioxidant mutual prodrugs were synthesized to obtain the prodrugs with expectations of improved anti-inflammatory and analgesic activity and devoid of ulcerogenicity. For this purpose the prepared prodrugs were evaluated for anti-inflammatory, analgesic and gastrointestinal ulceration properties. The experimental protocols were approved by Institutional Animal Ethics Committee (IAEC) and a written permission from in house ethical committee has been taken to carry out (Reference no. SCOP/2017/IAEC/10/02) and complete this study.

**Anti-inflammatory activity:** The parent drug ketoprofen in the dose of 20 mg/kg of body weight was used as reference standard. The doses of the prodrugs were selected on equimolar bases as shown in Table-2. They were tested for anti-inflammatory activity using Carrageenan induced hind paw edema method [27]. The edema is presented as the percentage increase in left hind paw in comparison to the uninjected right hind paw. Albino rates of either sex, weighing 200-250 g were selected & divided into 6 groups of each. Paw edema was induced in rats by means of subplantar injection into the left hind paw of rats by injecting freshly prepared solution of type IV, 0.1 mL of 1% carrageenan suspension under the plantar region of the left hind paw. In the right paw, saline (1 mL, 0.9%) was injected, which served as the control for comparison. Ketoprofen and other test drugs were administered orally 1 h before the irritant. The paw volume up to a fixed mark at the level of lateral malleolus was measured using plethysmometer after 2 h, 4 h of the carrageenan injection. Increase in paw volume was calculated as:

\[
\text{Increase in paw volume (\%)} = \frac{V_L - V_R}{V_R} \times 100
\]

\(V_L = \text{Volume of left paw, } V_R = \text{Volume of right paw (control).}\)

The mean ± SEM values were calculated for each group for the % edema. The results of left hind paw edema test are as given in Table-2. The prodrugs K.V.S. and K.G.S. showed comparable activity to that of standard (ketoprofen) while the prodrugs K.M.S and K.T.S. showed significantly smaller activity as compared to standard (ketoprofen) which may be due to low antioxidant profile of menthol/thymol promoieties, respectively.

**Analgesic activity studies:** NSAIDs are widely used for their peripheral analgesic properties. The most commonly used methods for measuring peripheral analgesic activity are the writhing tests in mice. Peripheral analgesic activity was determined against acetic acid induced writhing assay [28,29]. Writhing was induced by intra peritoneal (i.p.) injection of freshly prepared acetic acid solution (1 % w/v in saline pH = 2.7, 10 mL/kg, i.p.). The rats were divided into different treatment groups as shown in Table-3 containing six animals in each group. The test prodrug derivatives were administered the equimolar doses of ketoprofen (20 mg/kg, p.o.). All these were administered by oral route, emulsified in 0.5 % sodium carboxy methyl cellulose (sodium CMC) vehicle, 30 min prior to i.p. acetic acid. Animals were immediately transferred individually into glass chambers and a number of writhes (constriction of abdomen, turning of the trunk and extension of hind limbs) were recorded for 20 min, beginning 3 min after injection of acetic acid. The average number of writhes in each group of drug treated rats was compared with that of the control group and degree of analgesia was expressed as % inhibition.

\[
\text{Inhibition (\%)} = \left(1 - \frac{N_c}{N_t}\right) \times 100
\]

where, \(N_c = \text{Average number of writhes in control, } N_t = \text{Average number of writhes in drug treated rats.}\)

The control group (vehicle treated group) showed an average writhing of 78 ± 1.52. Ketoprofen showed significant inhibition in writhing at 20 mg/kg dose. The results are shown

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**TABLE-2**

**ANTI-INFLAMMATORY AND ANALGESIC EFFECT STUDIES OF WITH-SPACER-ESTER PRODRUGS OF KETOPROFEN**

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Treatment</th>
<th>Dose (mg/kg)</th>
<th>% Increase in paw volume mean ± SEM 2 h</th>
<th>% Increase in paw volume mean ± SEM 4 h</th>
<th>% Inhibition in writhings ± SEM</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Standard (ketoprofen)</td>
<td>20%</td>
<td>20.38 ± 1.87*</td>
<td>22.53 ± 0.92*</td>
<td>71.59 ± 1.25</td>
</tr>
<tr>
<td>II</td>
<td>K.T.S (ketoprofen-OCH2COO-thymol prodrug)</td>
<td>34.94</td>
<td>24.17 ± 1.54*</td>
<td>29.52 ± 1.42*</td>
<td>58.72 ± 1.47</td>
</tr>
<tr>
<td>III</td>
<td>K.G.S (ketoprofen-OCH2COO-guaiacol prodrug)</td>
<td>32.90</td>
<td>21.91 ± 0.61*</td>
<td>24.54 ± 1.07*</td>
<td>66.01 ± 1.03</td>
</tr>
<tr>
<td>IV</td>
<td>K.M.S (ketoprofen-OCH2COO-menthol prodrug)</td>
<td>35.42</td>
<td>29.65 ± 1.20*</td>
<td>32.71 ± 1.46*</td>
<td>56.12 ± 0.73</td>
</tr>
<tr>
<td>V</td>
<td>K.V.S (ketoprofen-OCH2COO-vanillin prodrug)</td>
<td>35.10</td>
<td>21.61 ± 1.32*</td>
<td>23.68 ± 0.78*</td>
<td>65.94 ± 1.32</td>
</tr>
<tr>
<td>VI</td>
<td>Control (CMC)</td>
<td>0.5</td>
<td>49.65 ± 1.36</td>
<td>69.05 ± 1.28</td>
<td>–</td>
</tr>
</tbody>
</table>

*P < 0.05 as compared to control, °P < 0.05 as compared to standard (ketoprofen); CMC: carboxy methyl cellulose

---

**TABLE-3**

**GRADES FOR THE OBSERVED LESIONS**

<table>
<thead>
<tr>
<th>Grades</th>
<th>Lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>[0]</td>
<td>Normal coloured stomach</td>
</tr>
<tr>
<td>[0.5]</td>
<td>Red colouration</td>
</tr>
<tr>
<td>[1.0]</td>
<td>Spot ulcers</td>
</tr>
<tr>
<td>[1.5]</td>
<td>Hemorrhagic streaks</td>
</tr>
<tr>
<td>[2.0]</td>
<td>Ulcer &gt;3 but &lt;5</td>
</tr>
<tr>
<td>[3.0]</td>
<td>Ulcers &gt;5</td>
</tr>
</tbody>
</table>

The control group (vehicle treated group) showed an average writhing of 78 ± 1.52. Ketoprofen showed significant inhibition in writhing at 20 mg/kg dose. The results are shown.
in Table-2. The equimolar doses of prodrugs K.T.S and K.M.S. showed lower analgesic activity as compared to the standard (ketoprofen). The other prodrugs showed comparable activity to that of the standard (ketoprofen).

**Anticancer/gastrointestinal erosion assay (GIERS):** Albino rats were distributed at random in different groups of 6 animals each (150-250 g). The animals were treated with ketoprofen (80 mg/kg) and test compounds by oral route four times of their anti-inflammatory activity once daily for 4 days. The compounds were administered as a suspension in 0.5% CMC in a volume of 0.5 mL/100 g of animal weight. The food was removed following the last dose on the fourth day. The animals were sacrificed using chloroform/ether fumes. At necropsy, the stomach was removed and opened along the length of greater curvature and were examined under the dissecting microscope for lesions (Tables 3 and 4) [30].

**Antioxidant studies (in vitro):** NSAIDs induced gastrointestinal pathogenesis is primarily due to their inherent property of inhibition of synthesis of those prostaglandins which induce the synthesis of protective mucus. And another proven reason is the generation of ROS (reactive oxygen species) which play role in pathogenesis gastrointestinal ulceration. The ester prodrugs of NSAIDs with phytophenols/alcohol are prepared with the aim to have antioxidant action of phytophenols/alcohol to counteract this side effect of NSAIDs. Antioxidant studies (in vitro) were done (Table-5) to find out whether the prepared prodrugs possess antioxidant properties. DPPH Assay was carried out [32] to assess the free radical scavenging activity of ketoprofen –OCH₂COO- phytophenols/prodrugs using 1,1-diphenyl-2-picrylhydrazyl radical (DPPH), which is a stable free radical having a purple colour. On reduction (with antioxidant) DPPH is reduced & its colour changed to yellow. IC₅₀ values are used to quantify the antioxidant activity. IC₅₀ value is the concentration of the sample (µg/mL) required to scavenge 50 % DPPH free radical and was calculated from the inhibition curve.

<p>| Table-4: ACUTE ANTIULCER/GASTROINTESTINAL EROSION ASSAY (GIERS) STUDIES |
|--------------------------------|------------------|---------------------|</p>
<table>
<thead>
<tr>
<th>S. No.</th>
<th>Treatment</th>
<th>Molar equivalent dose (mg/kg, p.o.)</th>
<th>Ulcer index (Mean ± SEM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Standard (Ketoprofen)</td>
<td>80*</td>
<td>4.27 ± 0.63*</td>
</tr>
<tr>
<td>II</td>
<td>K.T.S (Ketoprofen-OCH₂COO-Thymol prodrug)</td>
<td>139.76*</td>
<td>2.64 ± 0.20*</td>
</tr>
<tr>
<td>III</td>
<td>K.G.S (Ketoprofen-OCH₂COO-Guaiacol prodrug)</td>
<td>131.6*</td>
<td>1.88 ± 0.54*</td>
</tr>
<tr>
<td>IV</td>
<td>K.M.S (Ketoprofen-OCH₂COO-Menthol prodrug)</td>
<td>141.16</td>
<td>2.93 ± 0.41*</td>
</tr>
<tr>
<td>V</td>
<td>K.V.S (Ketoprofen-OCH₂COO-Vanillin prodrug)</td>
<td>140.40</td>
<td>1.57 ± 0.34</td>
</tr>
<tr>
<td>VI</td>
<td>Control</td>
<td>0.5 %</td>
<td>0.18 ± 0.06</td>
</tr>
</tbody>
</table>

*P < 0.05 as compared to control, *P < 0.05 as compared to standard

**Inhibition curves:** A 100 µM solution of DPPH in methanol was added to the separate solutions of thymol (10-100 µg/mL), guaiacol (10-100 µg/mL), menthol (10-100 µg/mL). Vanillin (10-100 µg/mL). The absorbance was read at 515 nm after 20 min. The radical scavenging activity was expressed as the percent inhibition and monitored as:

\[
\text{DPPH radical scavenging} (\%) = \frac{A_c - A_s}{A_c} \times 100
\]

\(A_c = \text{Absorbance of control (i.e. of DPPH without sample solution)}\)
\(A_s = \text{Absorbance of sample solution}\)

**RESULTS AND DISCUSSION**

The results of anti-inflammatory, analgesic and anticancer activity studies of ketoprofen and its mutual prodrugs with natural antioxidants though the –CH₂COO- spacers showed that there is a definite advantage of administering the prodrugs especially if used for the treatment of chronic inflammatory disorders like rheumatoid arthritis, osteoarthritis, Alzheimer’s disease, cancer, etc. This may be due to the improved physico-chemical properties, the gastro-protective/gastro-sparing properties due to masking of free –COOH group of the parent NSAID, better protection against the damages caused by ROS due to the release of antioxidants, thus ensuring better patient compliance hence the success of therapy. Moreover, it has been reported in the literature that conversions of conventional NSAIDs to the esters derivatives (increasing the size of the drug molecule which fits into COX-2 active site but not into COX-1 site) increase their COX-2 selectivity. This explains their better analgesic and anti-inflammatory activities with reduced gastrointestinal-toxicities.

**CONFLICT OF INTEREST**

The authors declare that there is no conflict of interests regarding the publication of this article.

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