Synthesis, *In Vitro* and *In Vivo* Evaluation of Morpholinoalkyl Ester Prodrugs of Niflumic acid

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**ABSTRACT:** Morpholinoalkyl ester prodrugs (2a-2c) of niflumic acid (1) were synthesized and evaluated *in vitro* and *in vivo* for their potential use for oral delivery with an aim to reduce its gastrointestinal side effects. The synthesized ester prodrugs were evaluated for solubility, partition coefficient, chemical and plasma hydrolysis, *in vivo* anti-inflammatory and gastrointestinal toxicity studies. Prodrugs showed a minimum of a 100-fold increase in solubility over the parent drug and also found to be more lipophilic. The hydrolysis followed pseudo-first order kinetics and resulted in a quantitative reversion to 1 by either chemical and/or enzymatic means. All prodrugs exhibited maximum anti-inflammatory comparable to 1 and were significantly less irritating to gastric mucosa than 1.

**Keywords:** Niflumic acid; morpholinoalkyl ester prodrug; human plasma hydrolysis; ulcerogenicity; anti-inflammatory activity.

**INTRODUCTION**

Niflumic acid (1) is a member of a group of compounds known as the fenamates and is a potent nonsteroidal anti-inflammatory drug (NSAID)¹,² used for the relief of pain and pyrexia. The mechanism of its anti-inflammatory action is based on inhibition of cyclooxygenases; these results in antipyretic, analgesic and anti-inflammatory effects.³,⁴ The therapeutic daily dose of fenamates varies from 200 to 1200 mg. As with other NSAIDs, the most common adverse effects reported with 1 are nausea, vomiting, peptic ulceration, gastric bleeding, abdominal pain, dyspepsia and diarrhea. About 30% of patients experience gastrointestinal side effects at therapeutic doses.⁵ The side effects are dose related and disappear on stopping the drug.⁶ However it is widely used in rheumatic disorders such as ankylosing spondylitis, osteoarthritis⁷ and rheumatoid arthritis.

GI mucosal injury produced by 1 and other NSAIDs is generally believed to be caused by two different mechanisms.¹⁰-¹³ The first mechanism involves a local action comprised of a direct contact mechanism and an indirect effect on the GI mucosa. The direct contact effect can be attributed to a combination of local irritation produced by acidic group of the NSAIDs and local inhibition of prostaglandin synthesis in the GI tract. The indirect effect can be attributed to a combination of an ion-trapping mechanism of NSAIDs in mucosal cells and back diffusion of hydrogen ions from the lumen into the mucosa. The second mechanism is based on a generalized systemic action occurring after absorption, which can be demonstrated following intravenous dosing.

Recently, considerable attention has been focused on the development of bioreversible derivatives, such as prodrugs, to temporarily mask the acidic group of NSAIDs as a promising means of reducing or abolishing the GI toxicity due to the local action mechanism.


![Chemical structure diagram](image)

Gu et al.\textsuperscript{14} evaluated kinetics of chemical and enzymatic hydrolysis of glycerol, glycolic acid and morpholinoethyl esters of a developmental analgesic agent. The aqueous shelf-lives of all the esters were <2 years at all pH values studied. No GI toxicity was reported for these prodrugs.

Kihel, L. et al.\textsuperscript{15} have reported the lipophilic prodrug of 1, and evaluated its anti-inflammatory effect in brain edema by determination of the prostaglandin E2 brain (PGE\textsubscript{2}) tissue concentration. 1 and its prodrug showed a marked anti-inflammatory activity at low concentration. Kim, H. et al.\textsuperscript{16} reported talinflumate, a prodrug of 1.

The present work was initiated to develop prodrugs of possessing a high enzymatic bioconversion rate and favorable physicochemical properties. Morpholinoethyl ester of different drugs have been prepared and shown to combine high water solubility and lipohilicity with adequate stability and a high susceptibility to undergo enzymatic hydrolysis in plasma.\textsuperscript{14,17} In the present work, a series of morpholinoalkyl ester of 1 were synthesized and evaluated in vitro and in vivo for the potential use as prodrugs for oral delivery. The physicochemical properties, plasma catalysed hydrolysis and GI toxicity of these derivatives are reported.

RESULTS AND DISCUSSION

Synthesis: Prodrugs of 1 were synthesized by standard procedure (Scheme 1). The percent yield, analytical data, and melting points of prodrugs and parent drug are listed in Table 1. The sharp melting points indicate that the morpholinoalkyl esters of 1 are crystalline compounds.

Analysis: The physicochemical properties of 1 and its prodrugs are shown in Table 2. The aqueous solubility of prodrugs at pH 1.3 (SGF) and pH 7.4 (phosphate buffer) were significantly greater than that of the parent drug. The solubility was increased by a minimum of 50-fold over the parent drugs. Apparent partition coefficient study in oct/SGF and oct/7.4 buffer revealed increase in lipophilicity (log P) value as compared to parent drug (Table 2). This indicate that all prodrugs are more lipophilic compared with parent drug. An increase in carbon chain length rendered prodrug more lipophilic; a ~1.6 fold increase in log P was observed from methyl to propyl derivative at pH 1.3, and a ~2.2 fold increase from methyl to propyl derivative at pH 7.4. Thus, one can expect better absorption of these prodrugs in vivo.

The kinetics of chemical and enzymatic hydrolysis of all prodrugs displayed pseudo-first-order kinetics over several half-lives. The half-lives and the rate constants for prodrug hydrolyses (Table 3) indicated that an increase in carbon chain length rendered the prodrugs more stable at pH 7.4, but less stable at pH 1.3. At pH 1.3, all prodrugs exist primarily as protonated species. Hence, an increase in the carbon chain length probably facilitates hydrolysis due to a change in transition state and an added inductive effect. The inductive effect increases with an increase in carbon chain length between the ester moiety and the morpholine function. This could probably be due to the release of electrons by additional alkyl groups, which weakens the ester bond with increasing distance from the protonated morpholino group. At pH 1.3, increasing the carbon chain length from methyl to propyl rendered the prodrug more labile to hydrolysis, which was indicated by a two fold increase in rate constant. A further increase in carbon chain length from ethyl to propyl did not result in a significant change in rate constant. Conversely at pH 7.4, an increase in carbon chain length from methyl to ethyl rendered the prodrug more stable; there is two fold decreases in rate constant. On
the other hand, an increase in carbon chain length from ethyl to propyl decreased the rate constant by ~3 fold. The enzymatic reactivity appears to depend predominantly on the carbon chain length between the ester and the morpholine function.

**Pharmacokinetic Evaluation** Based on *in vitro* evaluation, prodrugs were evaluated for anti-inflammatory and *in vivo* ulcerogenicity. All the prodrugs exhibited maximum anti-inflammatory activity at 3 h and the percentage inhibition was comparable (45-55%) with that of parent drug (Table 4). This reveals that the *in vivo* release of 1 is quantitative.

All prodrugs were tested for its ulcerogenicity potential because they were stable for at least 3 h in SGF. These esters also exhibited a rapid bioconversion to the parent compound in human plasma at 37 ± 0.5 °C. A gross observation of rat stomach indicated wide spread hemorrhage in rats treated with parent drug due to gastric mucosal injury following a single dose. Further, upon administration of a chronic dose, pale stomach with a paper thin structure and large ulcers were observed. The paleness was probably due to excessive bleeding during the study period of 4 days. The membranes of rats treated with prodrug, either single dose or chronic dose, showed no significant gastric mucosal injury and were similar to that of control. As shown in Fig. 1, the severity indices for prodrugs ranged from 0.40 ± 0.16 to 0.96 ± 0.35 while that of 1 was 2.21 ± 0.52, following a single dose. Following the chronic dose, the severity indices for prodrugs were ranged from 0.54 ± 0.21 to 1.16 ± 0.50 while that of 1 was 2.63 ± 0.41. Thus, the synthesized prodrugs of 1 exhibited minimum ulcerogenicity. As the prodrugs remained intact for at least 3 h in SGF, it can be assumed that they were absorbed intact, hence eliminating the local irritation produced by free carboxylic group. Moreover, the indirect effect of ion-trapping resulting in back diffusion of hydrogen ions from the lumen into the mucosal cells should be minimal as the prodrugs are not appreciably lipophilic in SGF. Although the intestinal mucosa was also examined, no detectable ulcers were noted. However, the complete elimination of ulcer formation cannot be avoided, since the prodrug conversion avoids the direct contact mechanism of acidic group, while the other route of ulcer formation continues to play significant role involving decreased tissue prostaglandin production that undermines the physiological role of cytoprotective prostaglandin in maintaining gastro-intestinal health and haemostasis. Hence, the future strategies of prodrug designing of a NSAID should focus on both the mechanism to eliminate ulcerogenic property associated with this drug.

## EXPERIMENTAL SECTION

### Materials

All melting points were determined by open capillary method and are uncorrected. Niflumic acid was purchased from Sigma Chemical, Germany. Human plasma was procured from the Mitra industries Ltd., Haryana, India. All other chemicals and reagents were of analytical grade and used as received. Distilled deionized water was used in the preparation of buffer solutions and mobile phases. IR spectra were recorded in KBr disks with Impact 410 FTIR Nicolet spectrometer. 1H NMR spectra were recorded on an EL Varian 300 MHz instrument. Chemical shifts are reported in parts per million (δ) relative to tetramethylsilane (1%) as the internal standard. UV/Visible spectra were taken on JASCO V-530 UV/Visible spectrophotometer. Column chromato graphy was accomplished using silica gel (30-60 μm). TLC was performed on glass plate coated with silica gel 60 F254, 0.2 mm thickness. The purity of the compound has been determined by HPLC method using Jasco HPLC with PU-2080 intelligent pump and UV-975 detector. The HPLC software used was Jasco Borwin Chromatograph (1.5 Version). The HPLC column used was RP C-18 (Thermo Electron Corporation, 250 x 4.6 mm, 5 μm). It was also used for analysis of plasma hydrolysates samples. Adult albino rats (180-210 g) of either sex were used in the anti-inflammatory and ulcerogenic studies.

### Synthesis

#### Synthesis of morpholinoalkyl esters of niflumic acid

General method for synthesis of morpholinoalkyl esters 2 is depicted in Scheme (1).18 Compound 1 (2.82 g, 0.01 mmol), was dissolved in methylene chloride (50 ml), and 4-(1-hydroxyalkyl)morpholine (0.01 mmol), dimethylaminopyridine (0.044 g, 0.68 mmol) and dicyclohexylcarbodiimide (2.3 g, 20.5 mmol) were added to the solution. The reaction mixture was stirred overnight in an ice bath at 0-5 °C in the presence of a drying tube. The precipitated dicyclohexylurea was filtered, and the solvent was evaporated under reduced pressure to obtain yellow oil. It was subjected to column chromatography using silica gel (30-60 μm) as adsorbent and hexane: acetone (2:3) as solvent to yield a free base as an oil. The oil was dissolved in ethanol and hydrogen chloride gas was passed into the solution. Removal of the precipitated solid by filtration, followed by recrystallization, yielded crystalline product. IR (KBr) data of all esters exhibited C=O ester peak around 1760-1720 cm⁻¹ confirming the formation of esters.

### Analysis

#### HPLC analysis

A reversed-phase HPLC procedure was used for the quantitative determination of esters and the parent compound. A mobile phase consisting
of acetonitrile and phosphate buffer (70:30, pH 7.32) with 0.004 M triethylamine was used for the analysis of I and its esters. The flow rate was 1.0 ml/min and the column effluent was monitored at 274 nm, with butyl paraben (BP) as the internal standard. The retention times for 1, 2a, 2b, 2c and BP were found to be 2.41, 2.53, 2.59, 2.83, and 4.2 min, respectively.

Determination of apparent partition coefficients

Apparent partition coefficients (P) of I and its prodrug were determined in n-octanol/SGF and n-octanol/pH 7.4 buffer at 25 ± 0.2 °C. Mutually pre-saturated phases were used. The traditional shake flask method was used, and concentrations were determined by HPLC to afford rapid evaluation and better reliability. The compounds were dissolved in octanol (5 ml) in screw capped test tubes. After addition of buffer (10 ml), the two phases were mixed on a shaking water bath maintained at 25 °C for 8 h. The tubes were centrifuged at 3000 rpm for 30 min. The octanol layer was removed, diluted; 20 μl of the resulting solution was injected into the HPLC column and peak area was measured (AUC<sub>octanol</sub>). The buffer solution was also removed, diluted, 20 μl of this solution was injected and corresponding peak area was obtained (AUC<sub>buffer</sub>). The partition coefficient (P) was determined from the following expression.

\[
P = \left( \frac{\text{AUC}_{\text{octanol}}}{\text{AUC}_{\text{buffer}}} \right) \times \text{dilution factor}
\]

Determination of solubility in simulated gastric fluid (SGF) and pH 7.4 phosphate buffer

The solubility of esters and the parent compounds were determined in SGF and pH 7.4 phosphate buffer at 25 ± 0.2 °C. The esters were freely soluble in both aqueous media. The solubility of I was determined at 25 ± 0.2 °C by adding excess amount of compound to the aqueous media in screw-capped test tube. The mixture was shaken on a mechanical shaker for 48 h to ensure equilibrium. Upon filtration through 0.45 μm nylon filters, an aliquot of the filtrate was diluted with mobile phase, mixed with the internal standard, and analyzed by HPLC. Six determinations were made and the mean value was calculated.

Kinetics of hydrolysis in human plasma

The hydrolysis of prodrugs was examined in human plasma diluted to 80% with 0.05 M phosphate buffer at pH 7.4 at 37 ± 0.5 °C. The reaction was initiated by adding 5 μl of stock solution (0.01 M) of the prodrug in acetonitrile to 5.0 ml of preheated plasma solution. The solutions were kept in water bath at 37 ± 0.5 °C and at appropriate time intervals, 250 μl samples were withdrawn and added to 1 ml of acetonitrile spiked with internal standard. After immediate mixing and centrifugation for 5 min at 6000 rpm, 20 μl of the clear supernatant was analyzed by HPLC for residual prodrug and parent drug. The rate constants for hydrolysis of the prodrugs were determined. Triplicate samples were analyzed and the mean value of rate constant was calculated.

Kinetics of hydrolysis in aqueous solutions

Reactions were initiated by adding 100 μl of a 0.01 M stock solution of prodrugs to 10 ml of SGF and pH 7.4 buffers in screw-capped vials that were pre-equilibrated at 37 ± 0.5 °C. The reaction was monitored by HPLC for residual prodrug and parent drug concentrations. Rate constants for the hydrolysis of prodrugs were determined from the slopes of linear plots of the logarithm of residual prodrug concentration versus time. Triplicate samples were analyzed, and the mean value of the rate constant was calculated.

Pharmacokinetic Evaluation

In vitro anti-inflammatory activity

The animal study protocols have met with the Institutional Animal Ethics Committee’s approval. Carrageenan induced rat hind paw edema method was used for determining anti-inflammatory activity. Albino rats (180-210 g) of either sex were taken in groups of six animals each. The synthesized compound was suspended in 1% solution of carboxy methyl cellulose (CMC) in distilled water. For control 1% solution of CMC in distilled water was given orally. Niflumic acid 20.0 mg/kg was used as reference drug. Thirty minutes after the drug administered, 0.1 ml of 1% w/v carrageenan solution was injected in the plantar region of the left hind paw of the animals. The inflammation was determined using a plethysmograph 3 h after injecting the phlogistic agents and compared with that of the control. The data was analyzed using student’s “t” test and the level of significance was defined at p<0.05. Data are expressed as mean ±SEM.

In vivo ulcerogenic study

Male albino rats (n = 6, 120-140 g) were used. They were fasted for 12 h prior to administration of drug solutions and for 4 h post dosing. Food was available at all other times, and free access to water was provided throughout the experiment. One group of rats (control) received no drug treatment, whereas other groups received either the parent drug or the prodrug. The following solutions in saline were administered orally: (1) the sodium salt of I; (2) Synthesized esters (2a-2c). Doses of 1 equivalent to 6.75 mg/kg were used. The rats were subjected to a single-dose and chronic-dose (same daily dose for 4 days) treatment. At 24 h following the last dose of chronic treatment and 4 h after the single dose, the rats were sacrificed in a carbon dioxide
chamber. The stomach was dissected out of the body along with the first 5 cm of the intestine and rinsed with saline; then, the contents of the stomach were emptied. The stomach and the intestine were excised open along the greater curvature and gently wiped clean with a swab dipped in saline. The mucosal damage was examined grossly under a binocular magnifier. The severity of mucosal damage was assessed by modification of a previously reported rating scale and the score is given in parentheses:

- no lesions (0.0), punctiform lesions (lesions < 1 mm) (0.5),
- five or more punctiform lesions (1.0), one to five small ulcers (1-2 mm) (2.0),
- more than five small ulcers or one large ulcer (2-4 mm) (3.0),
- more than one large ulcer (<4 mm) (4.0).

Based on the severity of the mucosal damage, the specimen was assigned an ordinal score as per the scoring scheme. For example, a specimen with five punctiform lesions, two small ulcers, and one large ulcer was assigned a score of 3.0. However, the control specimen did not exhibit the formation of lesions or ulcers and thus given the score of 0. The scores were averaged and the mean score was tabulated as the severity index for the drug solution administered.

Statistical analysis (t test) was performed to test the significance of difference in severity index between the prodrug and parent drug.

### Table 1. Physical Characteristics of 1 and its Prodrugs

<table>
<thead>
<tr>
<th>Compd</th>
<th>Yield %</th>
<th>mp (°C)</th>
<th>Molecular Formula</th>
<th>Analysis, %</th>
<th>¹H-NMR (δ ppm)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Calcd</td>
<td>Found</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>C</td>
<td>H-NMR</td>
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<tr>
<td>1</td>
<td>--</td>
<td>201</td>
<td>C₁₃H₉F₃N₂O₂</td>
<td>C</td>
<td>--</td>
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<td></td>
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<td></td>
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<td>H</td>
<td>--</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>N</td>
<td>--</td>
</tr>
<tr>
<td>2a</td>
<td>58</td>
<td>199</td>
<td>C₁₉H₁₈F₃N₃O₃</td>
<td>56.11</td>
<td>9.1 (s, 1H, NH), 8.7-8.4 (m, 3H, Py),</td>
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<td></td>
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<td></td>
<td></td>
<td>56.05</td>
<td>7.7 (m, 4H, Ar), 2.6-2.8 (m, 6H,</td>
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<td></td>
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<td></td>
<td></td>
<td>4.10</td>
<td>3 x OCH₂, 3.41 (m, 4H, 2 x NH₂).</td>
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<td>2b</td>
<td>47</td>
<td>181</td>
<td>C₁₉H₂₀F₃N₃O₃</td>
<td>56.72</td>
<td>8.9 (s, 1H, NH), 8.6-8.3 (m, 3H, Py),</td>
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<td></td>
<td>56.65</td>
<td>7.8-7.6 (m, 4H, Ar), 2.88-2.68 (m, 8H,</td>
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<td>4.31</td>
<td>3.6-3.4 (m, 4H, 2 x NH₂).</td>
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<td>4.25</td>
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<td></td>
<td></td>
<td>10.55</td>
<td>10.48 (3 x OCH₂), 3.6-3.4 (m, 4H, 2 x NH₂).</td>
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<td>10.30</td>
<td>10.03 (4 x OCH₂), 3.6-3.4 (m, 4H, 2 x NH₂).</td>
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<tr>
<td>2c</td>
<td>43</td>
<td>157</td>
<td>C₂₀H₂₂F₃N₃O₃</td>
<td>57.31</td>
<td>9.3 (s, 1H, NH), 8.8-8.7 (m, 3H, Py)</td>
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<td>57.26</td>
<td>7.7-7.5 (m, 4H, Ar), 3.0-2.7 (m, 10H,</td>
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<td></td>
<td>4.52</td>
<td>3 x OCH₂, 3.6-3.5 (m, 4H, 2 x NH₂).</td>
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<td>1.03</td>
<td></td>
<td></td>
<td></td>
<td>4.45</td>
<td>3.6-3.5 (m, 4H, 2 x NH₂).</td>
</tr>
</tbody>
</table>

### Table 2. Physicochemical Properties of 1 and its Prodrug

<table>
<thead>
<tr>
<th>Compd</th>
<th>Log Pᵃ</th>
<th>Log Pᵇ</th>
<th>Sol M/Lᵃ</th>
<th>Sol M/Lᵇ</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.88 ± 0.12</td>
<td>0.46 ± 0.20</td>
<td>3.15x10⁻⁵ ± 4.016x10⁻⁶</td>
<td>3.38x10⁻⁵ ± 3.104x10⁻⁶</td>
</tr>
<tr>
<td>2a</td>
<td>0.98 ± 0.19</td>
<td>0.78 ± 0.24</td>
<td>1.66x10⁻³ ± 3.022x10⁻⁴</td>
<td>2.00x10⁻³ ± 4.029x10⁻⁵</td>
</tr>
<tr>
<td>2b</td>
<td>1.06 ± 0.31</td>
<td>1.16 ± 0.18</td>
<td>2.89x10⁻³ ± 2.011x10⁻⁴</td>
<td>2.78x10⁻³ ± 2.556x10⁻⁴</td>
</tr>
<tr>
<td>2c</td>
<td>1.55 ± 0.26</td>
<td>1.73 ± 0.32</td>
<td>2.23x10⁻³ ± 3.841x10⁻⁵</td>
<td>2.39x10⁻³ ± 2.018x10⁻⁴</td>
</tr>
</tbody>
</table>

ᵃ Apparent Log P in SGF. ᵇ Apparent Log P in pH 7.4 phosphate buffer.
Table 3. Kinetic Parameters for Hydrolysis of Prodrugs (2a-2c) at 37 °C

<table>
<thead>
<tr>
<th>Compd</th>
<th>$K_{obs}$ min$^{-1}$</th>
<th>$t_{1/2}$ h</th>
<th>$K_{obs}$ min$^{-1}$</th>
<th>$t_{1/2}$ h</th>
<th>$K_{obs}$ min$^{-1}$</th>
<th>$t_{1/2}$ h</th>
</tr>
</thead>
<tbody>
<tr>
<td>2a</td>
<td>0.018 ± 0.29x10$^{-3}$</td>
<td>38.5 ± 0.42</td>
<td>0.071 ± 0.68x10$^{-3}$</td>
<td>9.76 ± 0.15</td>
<td>0.32 ± 0.29x10$^{-2}$</td>
<td>2.16 ± 0.08</td>
</tr>
<tr>
<td>2b</td>
<td>0.056 ± 0.82x10$^{-3}$</td>
<td>17.37 ± 0.54</td>
<td>0.037 ± 0.49x10$^{-3}$</td>
<td>18.72 ± 0.27</td>
<td>0.42 ± 0.36x10$^{-2}$</td>
<td>1.63 ± 0.10</td>
</tr>
<tr>
<td>2c</td>
<td>0.043 ± 0.34x10$^{-3}$</td>
<td>16.11 ± 0.39</td>
<td>0.013 ± 0.51x10$^{-3}$</td>
<td>53.30 ± 0.31</td>
<td>0.25 ± 0.74x10$^{-2}$</td>
<td>2.73 ± 0.15</td>
</tr>
</tbody>
</table>

a In SGF (pH 1.3). b In pH 7.4 phosphate buffer. c In human plasma

Table 4. Anti-inflammatory activity of 1 and its prodrugs (2a-2c)

<table>
<thead>
<tr>
<th>Compd</th>
<th>Antiinflammatory activity ( % inhibition ± SEM of oedema over control)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 min</td>
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<tr>
<td>Control</td>
<td>-</td>
</tr>
<tr>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>2a</td>
<td>-</td>
</tr>
<tr>
<td>2b</td>
<td>-</td>
</tr>
<tr>
<td>2c</td>
<td>-</td>
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</table>

Fig. 1. Severity Index in Rats Following Single and Chronic Dose Oral Administration of 1 and its Prodrugs.
CONCLUSIONS

In vitro and in vivo evaluation indicated that the prodrugs were freely soluble, more lipophilic than parent drug, and were stable enough in SGF to be absorbed intact. In solid state, prodrugs were very stable at room temperature. Prodrugs were significantly less irritating than parent drug in rats, as determined by the severity of gastric mucosal injury, following single dose and chronic oral administration. In conclusion, morpholinoalkyl esters of 1 represent potentially useful derivatives to increase the solubility of 1 and to decrease gastrointestinal side effects without altering the pharmacological profile of the parent drug. These properties make the novel ester promising prodrug forms of 1 to improve oral delivery.

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