Ester Prodrugs of Ketoprofen: Synthesis, Hydrolysis Kinetics and Pharmacological Evaluation

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Key words
- ketoprofen
- ester prodrug
- dicyclohexyl carbodimide
- anti-inflammatory
- analgesic
- ulcerogenicity

Abstract

The ester prodrugs of ketoprofen with various naturally available antioxidants; menthol, thymol, eugenol, guiacol, vanillin and sesamol have been synthesized by the dicyclohexyl carbodiimide (DCC) coupling method, purified and characterized by spectral data. Further, their, partition coefficients have been determined as well as, hydrolytic studies performed. The synthesized compounds are more lipophilic compared to the parent moieties and are stable in acidic environment, which is a prerequisite for their oral absorption. Under gastric as well as intestinal pH conditions these prodrugs showed variable susceptibility towards hydrolysis. The title compounds when evaluated for anti-inflammatory, analgesic activities and ulcerogenicity, showed improvement over the parent drug.

Introduction

Non-Steroidal Anti-inflammatory Drug's (NSAIDs) are the most commonly used drugs worldwide today for the treatment of peripheral pain and inflammation. They act through the inhibition of the enzyme cyclooxygenase (COX). It is well established that 2 isoforms, cyclooxygenase-I (COX-I) and cyclooxygenase-II (COX-II) exist [1]. The potentially deleterious effects of NSAIDs on gastrointestinal tract are due to 2 reasons. a) They inhibit the cytoprotective COX-I and b) Their carboxylic acidic functionality has a direct irritant action on the GIT [1–3] and thus, their long term use leads to ulcers and bleeding [4,5] as well as, other gastric side effects [6]. Due to this some selective COX-II inhibitors devoid of the carboxylic acid functionality e.g., celecoxib, rofecoxib, etoricoxib and valdecoxib, have been introduced in clinical use. However, serious cardiovascular side effects arising on their long term use have led to the withdrawal of some of these drugs [7]. It is now well known that localized generation of reactive oxygen species (ROS) play important role in the gastric ulcerations associated with the NSAID therapy [8,9]. Thus, antioxidants can play a major role in the prevention of gastric ulcer formation. Several naturally occurring antioxidant compounds are considered promising in treatment of free radical mediated diseases [10]. Naturally occurring antioxidants like menthol, thymol, eugenol, guiacol, vanillin and sesamol can be considered as the suitable promoieties for mutual prodrugs as, besides masking the irritant carboxylic acid function, they provide the additional antioxidant effect [11–13]. Based on this rationale prodrugs of diclofenac [14], biphenyl acetic acid [15], ibuprofen [16,17] and mefenamic acid [18,19] with natural phenolic & alcoholic antioxidant compounds are reported.

Ketoprofen (KTP), an aryl propionic acid derivative is an effective non-steroidal anti-inflammatory drug. There are reports on the synthesis and evaluation of prodrugs of ketoprofen and various promoieties, like synthetic phenols, paracetamol, aminoacids, amines, hydroxyamines [20–25], as well as, polymeric compounds like, PEG, polyoxyethylene or vinylether polymers [26–28]. However, to the best of our knowledge the conjugation of naturally occurring phenolic/alcoholic compounds with ketoprofen is hitherto unreported.

In the present study, ketoprofen has been conjugated with thymol, menthol, eugenol, guiacol, vanillin and sesamol to obtain its ester prodrugs. The synthesized prodrugs have been characterized by spectral data. Further, they have been evaluated for physicochemical properties, like solubility, partition coefficient, hydrolytic stability. These title prodrugs have also been evaluated for anti-inflammatory, analgesic activity and ulcerogenic potential.

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Materials and Methods

Materials

Ketoprofen was obtained from Ozone Laboratories Ltd (Mumbai, India). Thymol, menthol, eugenol, guaicol, vanillin, dimethylaminopyridine and N, N'-dicyclohexyl carbodimide, as well as all other reagents and solvents were commercially procured from Loba Chemicals Pvt. Ltd. (Mumbai, India). IR spectra were recorded on a Bruker FT-IR spectrometer (Model – Alpha). The ^{1}H NMR spectra were recorded on Bruker AVANCE III HD 500 MHz spectrometer. The mass spectra were recorded on JEOL GCMATE II GC-MS system. The HPLC system used for determining the partition coefficient and hydrolysis studies of the compounds was Jasco PU-2089 plus Quaternary model with a UV/Vis detector and a C-18 column (Finepak SIL, 250×4.6 mm, 5 µm). The HPLC software used was Jasco-ChromNAV (1.19.1 Version). Digital plethysmometer (UGO-BASILE-7140 Barcelona, Italy) was used for anti-inflammatory studies.

Methods

Synthesis of ketoprofen prodrugs: general procedure

To a well stirred and cooled solution of ketoprofen (0.885 g, 2.5 mmol) in dichloromethane (50 ml), the appropriate alcohol/phenol (2.5 mmol) was added at 0 °C, followed by N, N'-dicyclohexyl carbodimide (0.515 g, 2.5 mmol) and dimethylaminopyridine (0.012 g, 0.1 mmol) over 30 min. The reaction mixture was thereafter, allowed to stir at 0 °C for 1 h and at room temperature for next 12 h. The reaction mixture was filtered thereafter, to separate the precipitated N, N'- dicyclohexyl urea. The filtrate was washed with aq. 5 % w/v $NaHCO_3$ solution (25 ml × 2). The aqueous layer was separated and organic layer washed aq. 5% w/v NaOH solution (5 ml × 2). The organic layer was dried (Na_2SO_4) and the solvent distilled out under reduced pressure. The crude product was purified by column chromatography using hexane-ethyl acetate as eluent [29] ◉ **Fig. 1**.

(3-Benzoylphenyl)propionic acid, 5-isopropyl-2-methylphenyl ester (KTPTH)

UV (λ_{max}): (MeOH) 261 nm, IR (KBr) cm^{-1}: 3033 (C-H str. aromatic), 2930 and 2850 (C-H str. aliphatic), 1754 (C=O str. ester), 1243 (C-O str. ester), 1626 (C=C str. aromatic), 1283 (C-H bending In plane), 895 (C-H bending out of plane). ^{1}H NMR (500 MHz, DMSO): δ 1.03–1.27 (m, 6 H, 2CH_3), δ 1.57–1.58 (d, 3 H, -C-CH_3), δ 2.24 (s, 3 H, Ar-CH_3), δ 3.11–3.16 (m, 1 H,CH_3-CH-CH_3), δ 4.27–4.31 (m, 3 H, -CH-CH_3), δ 6.79 (s, 1 H, Ar-H), δ 7.01–7.02 (d, 1 H Ar-H), δ 7.16–7.17 (d, 1 H, Ar-H), δ 7.54–7.62 (m, 4 H, Ar-H), δ 7.66–7.77 (m, 2 H, Ar-H), δ 7.76–7.77 (m, 2 H, Ar-H), δ 7.80 (s, 1 H, Ar-H). Mass: (70 eV) m/z 386.

(3-Benzoylphenyl)propionic acid, 5-isopropyl-2-methylcyclohexyl ester (KTPME)

UV (λ_{max}): (MeOH) 260 nm, IR (KBr) cm^{-1}: 3033 (C-H str. aromatic), 2929 and 2852 (C-H str. aliphatic), 1729 (C=O str. ester), 1245 (C-O str. ester), 1626 (C=C str. aromatic), 1282 (C-H bending In plane), 896 (C-H bending out of plane). ^{1}H NMR (500 MHz, DMSO): δ 0.90–1.05 (m, 6 H, -CH_2-), δ 1.20–1.33 (m, 6 H, 2CH_3), δ 1.48–1.55 (d, 3 H, -C-CH_3), δ 1.58–1.59 (d, 3 H, -CH_3), δ 3.89–3.93 (m, 1 H, -CH-CH_3), δ 4.48–4.60 (m, 1 H,CH_3-CH-CH_3), δ 7.53–7.54 (m, 1 H Ar-H), δ 7.55–7.56 (d, 1 H, Ar-H), δ 7.57–7.59 (m, 3 H, Ar-H), δ 7.60–7.64 (m, 2 H, Ar-H), δ 7.68–7.73 (m, 2 H, Ar-H). Mass: (70 eV) m/z 392.

2-(3-Benzoylphenyl)propionic acid, 5-allyl-2-methoxyphenyl ester (KTPEU)

UV (λ_{max}): (MeOH) 261 nm, IR (KBr) cm^{-1}: 3061 (C-H str. aromatic), 2932 and 2850 (C-H str. aliphatic), 1758 (C=O str. ester), 1282 (C-O str. ester), 1625 (C=C str. aromatic), 1282 (C-H bending In plane), 911 (C-H bending out of plane). ^{1}H NMR (500 MHz, DMSO): δ 1.53–1.54 (d, 3 H, -C-CH_3), δ 3.24–3.26 (d, 2 H, Ar-CH_2), δ 3.62 (s, 3 H,-OCH_3), δ 4.21–4.26 (q, 3 H, Ar-CH-CH_3), δ 4.99–5.12 (m, 2 H,=CH_2), δ 5.90–5.99 (m, 1 H, -CH=), δ 6.55–6.59 (m, 1 H, Ar-H), δ 6.72–6.76 (m, 1 H, Ar-H), δ 6.91–6.94 (m, 1 H, Ar-H), δ 752–7.61 (m, 4 H, Ar-H), δ 7.65–7.80 (m, 5 H, Ar-H). Mass: (70 eV) m/z 400.

2-(3-Benzoylphenyl)propionic acid, 2-methoxyphenyl ester (KTPGU)

UV (λ_{max}): (MeOH) 262 nm, IR (KBr) cm^{-1}: 3063 (C-H str. aromatic), 2975 and 2932 (C-H str. aliphatic), 1758 (C=O str. ester), 1258 (C-O str. ester), 1599 (C=C str. aromatic), 1282 (C-H bending In plane), 890 (C-H bending out of plane). ^{1}H NMR (500 MHz, DMSO): δ 1.54–1.55 (d, 3 H, -C-CH_3), δ 3.33 (s, 3 H, -OCH_3), δ 3.75

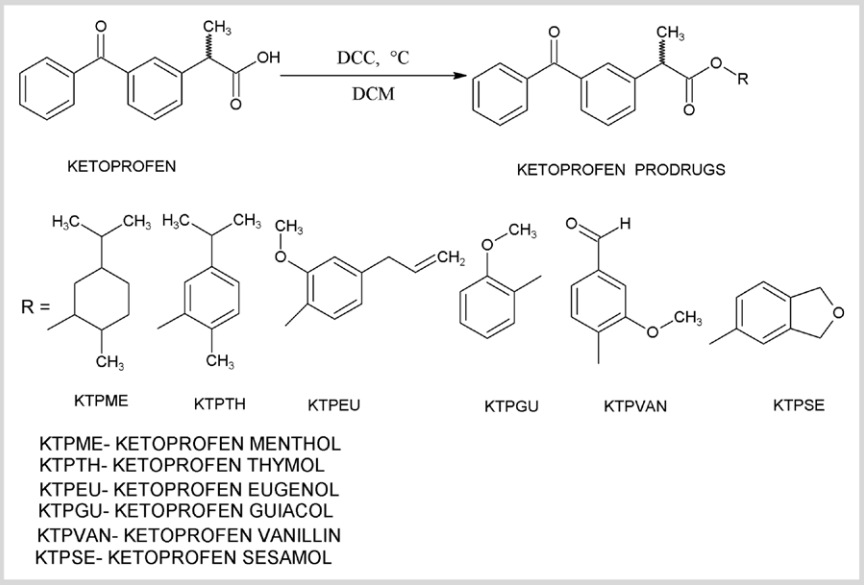

Fig. 1 Synthesis of ketoprofen prodrugs.

(s, 1H, -CH-CH_3), δ 6.58–6.59 (m, 1H, Ar-H), δ 6.73–6.76 (m, 1H Ar-H), δ 6.89–7.03 (m, 2H, Ar-H), δ 7.08–7.09 (m, 1H, Ar-H), δ 7.20–7.24 (m, 1H, Ar-H), δ 7.51–7.62 (m, 3H, Ar-H), δ 7.66–7.71 (m, 2H, Ar-H) δ 7.73–7.77 (m, 2H, Ar-H). Mass: (70 eV) m/z 376.

2-(3-Benzoylphenyl)propionic acid, 4-formyl-2-methoxyphenylester (KTPVAN)

UV (λ_{max}): (MeOH) 260 nm, IR (KBr) cm^{-1}: 3052 (C-H str. aromatic), 2933 and 2850 (C-H str. aliphatic), 1760 (C=O str. ester), 1212 (C-O str. ester), 1653 (C=C str. aromatic), 1288 (C-H bending In plane), 819.96 (C-H bending out of plane). ^{1}H NMR (500 MHz, DMSO): δ 1.39–1.40 (d, 3H, -C-CH_3), δ 3.81–3.82 (q, 1H, Ar-CH-CH_3), δ 3.84 (s, 3H, -OCH_3), δ 6.39 (d, 1H, Ar-H), δ 7.41–7.43 (d, 1H, Ar-H), δ 7.51–7.54 (t, 1H, Ar-H), δ 756–7.62 (m, 4H, Ar-H), δ 7.68–7.71 (m, 2H, Ar-H), δ 7.73–7.76 (m, 2H, Ar-H), δ 9.97 (s, 1H, -CHO). Mass: (70 eV) m/z 387.

2-(3-Benzoylphenyl)propionic acid 1,3-dihydroisobenzofuran-5-yl ester (KTPSE)

UV (λ_{max}): (MeOH) 262 nm, IR (KBr) cm^{-1}: 3061 (C-H str. aromatic), 2931 and 2852 (C-H str. aliphatic), 1754 (C=O str. ester), 1248 (C-O str. ester), 1601 (C=C str. aromatic), 1283 (C-H bending In plane), 893 (C-H bending out of plane). ^{1}H NMR (500 MHz, DMSO): δ 1.52–1.54 (d, 3H, -C-CH_3), δ 4.19–4.23 (q, 1H, Ar-CH-CH_3), δ 6.05 (s, 2H, -CH_2-, Sesamol), δ 6.46–6.48 (m, 1H, Ar-H), δ 6.67–6.69 (d, 1H Ar-H), δ 6.72–6.76 (m, 2H, Ar-H), δ 6.58–6.60 (d, 1H, Ar-H), δ 6.89–6.90 (d, 1H, Ar-H), δ 7.54–7.55 (m, 1H, Ar-H), δ 7.55–7.59 (m, 3H, Ar-H), δ 7.60–7.62 (m, 2H, Ar-H), δ 7.68–7.70 (m, 2H, Ar-H). Mass: (70 eV) m/z 378.

Solubility and Partition coefficient determination

10 mg of the synthesized prodrug was tested for solubility in 0.5 ml of each of the solvents, *viz.*, ethanol, methanol, chloroform and dichloromethane in separate test tubes. After gentle shaking, solubility was observed. Further, 0.5 ml of solvent was added if required to completely dissolve the compound. The partition coefficients of synthesized prodrugs were determined in n-octanol-phosphate buffer (1:1) (pH 7.4) as follows. The prodrug, 10 mg, was added to 10 ml of aqueous phase followed by addition of 10 ml of n-octanol. The contents were thoroughly shaken for 2 h at room temperature and left for 1 h. The concentrations in the aqueous and organic phase was determined using acetonitrile: phosphate buffer pH 3 (60:40 v/v) as mobile phase and flow rate 1.0 ml/min with UV detection at 260 nm by using HPLC [30] and partition coefficient computed.

In vitro hydrolysis

The hydrolysis kinetics of the prodrugs was studied in aqueous buffer solutions at pH 1.2 and pH 7.4 at 37 °C using hydrochloric acid-buffer and phosphate buffer, respectively. Solutions of 10 mg of the prodrug prepared in 90 mL of hydrochloric acid-buffer (pH 1.2) or phosphate buffer (pH 7.4) were kept in screw capped tubes maintained at 37 ± 0.5 °C. At definite time intervals (15, 30, 60, 120, 240 min), aliquots were withdrawn from tubes and analyzed by HPLC for the amount of drug released after the hydrolysis of the prodrug. Pseudo first order rate constants (K_{obs}) and half-life ($t_{1/2}$) were calculated [31].

Pharmacological evaluations

The title prodrugs were evaluated for analgesic, anti-inflammatory and ulcerogenic potential. Wistar rats (albino rats) of either sex weighing 100–200 g were divided into 8 groups of 6 animals each for the evaluation of anti-inflammatory activity and ulcerogenic potential and Swiss albino mice were used for the evaluation of analgesic activity. The animals were housed in standard polypropylene cages in an air-conditioned room at 22 ± 3 °C with 55 ± 5% humidity and provided with standard laboratory diet and water ad libitum. The study protocol was approved by Institutional Animal Ethics Committee (448/01/c/CPCSEA/PRCOP/14-15/12).

Anti-inflammatory activity

The anti-inflammatory activity of ketoprofen ester prodrugs was determined by using carrageenan-induced rat paw edema model [32,33]. Group I served as the control and received only vehicle (0.5% w/v aq.CMC suspension). Group II received ketoprofen (25 mg/kg) while, the groups III–VIII received prodrugs in the doses molecularly equivalent to ketoprofen, *p. o.* After 30 min of compound administration, 0.1 mL of 1% w/v carrageenan in normal saline was injected into the sub planter region of left hind paw and the edema volume was measured before injection and at the several intervals up to 12 h. The initial volume of right hind paw was measured using a digital plethysmometer without administration of drug/prodrug.

Analgesic activity

Analgesic activity was carried out by the acetic acid induced writhing method [34] using the swiss albino mice model. A 1% v/v aqueous solution of acetic acid was used to induce writhings. The animals of either sex were used and were divided in 8 groups of 6 animals each. Group I served as a control group, group II received standard drug, ketoprofen (25 mg/kg) and all other 6 groups received appropriate prodrugs in molecularly equivalent doses, orally, in a 1% w/v aqueous suspension of sodium carboxymethylcellulose. Acetic acid was administered intraperitoneally at 1 mL/100 g body weight of the animal. Test compounds were administered orally 3 h prior to acetic acid injection. The number of writhings in 10 min within the control group and the standard and test compounds groups, were counted and compared. Analgesic activity was measured as percentage decrease in writhing as compared to the control.

Ulcerogenic potential

Gastrointestinal toxicity of the synthesized prodrugs was compared with that of the parent drug, ketoprofen by measuring the ulcer index. For this albino Wistar rat of either sex, weighing around 100–150 g each, were divided in 8 groups of 6 animals each and fasted for 24 h prior to administration of drug/prodrug. The ketoprofen (standard, 250 mg/kg) and prodrugs (dose of prodrugs molecularly equivalent to ketoprofen) were administered orally as aqueous suspension in 0.5% w/v acacia. The control group was administered as 0.5% w/v acacia aqueous suspension only. Animals were sacrificed 12 h after the treatment. The stomach was removed, opened along the curvature, rinsed with 5 ml saline and examined by means of a magnifier. The ulcer index was calculated as mean for all animals in the group [35].

Statistical analysis

Statistical analysis was carried out for pharmacological evaluation data using analysis of variance (ANOVA) test, followed by Dunnet's Test for determining level of significance. P-values < 0.05 were considered statistically significant.

Results and Discussion

Chemistry

The ketoprofen ester prodrugs were synthesized by the DCC coupling method. Menthol, thymol, eugenol, guiacol, vanillin and sesamol were identified as promoieties for the synthesis of ketoprofen ester prodrugs. Purity of the synthesized prodrugs was ascertained by melting point and thin layer chromatography (TLC). The products were obtained in reasonable yields (66–75%). The title compounds were confirmed by FTIR, ^{1}H NMR and Mass spectroscopic data. The IR spectra of these compounds show characteristics C=O stretching bands around 1729–1760 cm^{-1} and C-O stretching bands around 1212–1282 cm^{-1} for the ester functionality. The ^{1}H NMR spectra exhibit the signals for the –CH- proton at δ 3.75–4.31 and $-CH_3$ protons around δ 1.39–1.58. Besides these, the signals characteristic to the functionalities of the promoieties appear lending confirmation to the structures assigned to the target prodrugs. The mass spectra of the title compounds reveal the molecular ion peaks as the base peaks.

Solubility and partition coefficient

The synthesized ketoprofen ester prodrugs were subjected to solubility studies. It was observed that while the parent drug, ketoprofen was highly soluble in 0.1 N sodium hydroxide solution, the prodrugs were found to be sparingly soluble in 0.1 N NaOH. All the prodrugs showed higher solubility than the parent drug in organic solvents such as methanol, ethanol, chloroform and dichloromethane indicating their lipophilic nature. A drug's partition coefficient is a measure of its distribution in a lipophilic/hydrophilic phase system, and is indicative of its ability to penetrate biological multiphase system. The Partition coefficients of ketoprofen ester prodrugs were higher as compared to parent drug ketoprofen (**Table 1**). With increase in log P that major fraction was partitioned toward the organic phase, indicates enhancement in the lipophilicity, favorable to biological absorption.

Table 1 Physical constants and physicochemical characteristics of ketoprofen prodrugs.

Prodrug	Yield (%)	Melting point (°C)[a]	Rf Value[b]	Partition coefficient
KTP	–	94–96	0.44	3.12
KTPTH	68.3	81–82	0.62	5.07
KTPME	77.2	77–79	0.52	5.91
KTPEU	75.4	65–67	0.71	4.89
KTPGU	72.6	58–60	0.49	4.78
KTPVAN	64.7	77	0.65	4.66
KTPSE	66.8	55–56	0.66	5.32

[a]Uncorrected; bTLC (Ethyl acetate: n-hexane: chloroform (5: 2: 1)

Table 2 Kinetic data for the hydrolysis of ketoprofen prodrugs at different pH at 37 °C.

pH	1.2		7.4	
Prodrug	K_{obs}	$t_{1/2}$ (h)	K_{obs}	$t_{1/2}$ (h)
KTPTH	1.347×10^{-3}	8.57	2.068×10^{-3}	5.58
KTPME	1.162×10^{-3}	9.92	1.847×10^{-3}	5.93
KTPEU	1.518×10^{-3}	7.57	3.238×10^{-3}	3.57
KTPGU	1.177×10^{-3}	6.80	2.637×10^{-3}	4.37
KTPVAN	1.794×10^{-3}	6.43	4.223×10^{-3}	2.75
KTPSE	1.586×10^{-3}	7.28	2.482×10^{-3}	4.65

Chemical stability

The hydrolysis kinetics of ketoprofen ester prodrugs was studied in aqueous buffer solution at pH 1.2 and pH 7.4 to confirm the extent of release of parent drug. The decrease in concentration of ester prodrugs was monitored by HPLC. The results showed longer half-life of prodrugs in acidic pH 1.2 as compared to pH 7.4, which implies that they may pass unhydrolyzed through stomach and possess enough stability to be absorbed from intestine. The values of the rate parameters K_{obs} for hydrolysis of prodrugs at different pH and 37 °C are listed in **Table 2** along with their half-lives ($t_{1/2}$). The chemical degradation of ester prodrugs of ketoprofen followed first order kinetics and were quantitatively converted to parent drug as revealed by HPLC analysis. In the acidic buffer solution of pH 1.2 all prodrugs showed high chemical stability which implied that the compounds passed unhydrolyzed through the stomach on oral administration. While, at neutral pH 7.4 their $t_{1/2}$ ranging from 165 min to 355 min.

Pharmacological evaluation

Synthesized prodrugs were evaluated for anti-inflammatory, analgesic and ulcerogenic potential. The prodrugs (in molecularly equivalent dose) showed higher or comparable inhibition of carrageenan induced inflammation than ketoprofen. Ketoprofen-eugenol prodrug showed higher anti-inflammatory activity than parent drug, which may be due to synergistic activity of eugenol. The prodrugs show retention of anti-inflammatory activity with percentage inhibition of 77–83% as compared to 81% when studied up to 12 h (**Table 3**). For analgesic activity, the decrease in number of writhings was expressed as a percentage protection from pain (analgesic activity) by test compounds with reference to control. The title compounds showed considerable retention of analgesic activity (55–70%) as compared to that of ketoprofen (64%) (**Table 3**). All the synthesized prodrugs showed lower ulcer index value as compared to ketoprofen, thus indicating decrease in gastrointestinal side effects through

Table 3 Anti-inflammatory, Analgesic and ulcerogenic activity of ketoprofen prodrugs.

Group	Anti-inflammatory activity (% inhibition)[a]				Analgesic activity (%)	Ulcer Index[b] (±SEM)
	2 h	4 h	6 h	12 h		
KTP (Standard)	51.29	58.80	69.56	81.27	64.97	3.244±0.153
KTPTH	46.27	55.41	72.54	83.61	67.97	2.398±0.158
KTPME	49.65	57.55	68.78	81.58	59.88	0.917±0.080
KTPEU	52.35	63.70	74.22	86.42	70.05	0.153±0.055
KTPGU	44.83	53.90	65.67	77.83	55.39	2.296±0.146
KTPVAN	50.13	59.93	70.21	82.98	60.78	3.215±0.140
KTPSE	45.31	55.03	68.01	79.24	60.48	3.075±0.141

[a]Statistical analysis was performed with ANOVA followed by dunnett test $P<0.05$ with respect to control

[b]Data represented as mean ± SEM, n = 6 for ulcer index

successful masking of free carboxylic group of drug. The data represents that the risk of gastric ulceration is reduced by 2–3 times in prodrugs as compared to ketprofen. Eugenol and menthol prodrugs caused lowest ulceration of GI tract.

Conclusion

Natural phytophenols and alcohols are good free radical scavengers/antioxidants and also exhibit NSAID type activites. In present study 6 such compounds were employed as promoieties to prepare the title ester prodrugs of ketoprofen. The title compounds were synthesized by dicyclohexylcarbodimide coupling and evaluated analgesic, antinflammatory activites and ulcrogenic potential, as well as hydrolysis kinetics. The aim and rationale behind the present study was of achieving synergistic effect and reducing gastrointestinal side effects associated with ketoprofen. The synthesized prodrugs showed improved solubility in organic solvents which implies their lipophilic character. They were found chemically stable, biolabile and showed comparable analgesic and anti-inflammatory activities to the parent drug, with reduced ulcerogenicity. Retention of activity along with reduction in ulcerogenicity may be due to analgesic properties of some phytophenols and prevention of direct contact of carboxylic group with gastric mucosa. The study shows that mutual prodrug approach can be successfully used in improving therapeutic effectiveness of NSAID's.

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Conflict of Interest

The authors confirm that this article content has no conflicts of interest.

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