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Novel ketoprofen–antioxidants mutual codrugs as safer nonsteroidal anti-inflammatory drugs: Synthesis, kinetic and pharmacological evaluation

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Abstract

Ketoprofen belongs to one of the most common nonsteroidal anti-inflammatory drugs (NSAIDs) but its clinical usefulness has been restricted due to the high incidence of gastrointestinal complications. The release of reactive oxygen species (ROS) in NSAIDs therapy plays a major role in causing gastric complications. Antioxidants not only prevent gastric ulceration and lipid peroxidation but also preserve glutathione-type peroxidase (GPO) activity. Therefore, the present study investigates the utility of combining anti-inflammatory and antioxidant properties of two different compounds in a single molecule to form a series of 16 ketoprofen–antioxidant mutual codrugs. The free carboxylic group, which is believed to be one of the reasons for gastric toxicity of ketoprofen, was masked temporarily by simple and double esterification with alcoholic/phenolic–OH of natural antioxidants. In simple esterification, ketoprofen is directly linked to natural antioxidants (**IIa–h**) in the hope to obtain drugs free of gastric side effects. In an attempt to improve the in vivo lability, as well as gastric side effects, the double ester codrugs, that is, ketoprofen–antioxidant through the glycolic acid spacer (–CH_2COO; **IIIa–h**), have also been designed and synthesized. The synthesized codrugs were characterized by IR, ^{1}H NMR, ^{13}C NMR, mass spectroscopy and elemental analysis. The in vitro hydrolysis studies showed the lowest hydrolysis (highest stability) in acidic pH 1.2, whereas moderate hydrolysis was seen at pH 7.4 and significant hydrolysis in 80% human blood plasma, as indicated by their $t_{1/2}$. The pharmacological evaluation results indicate that these ketoprofen–antioxidant mutual codrugs showed the retention of anti-inflammatory and analgesic activity with a significant reduction in the ulcer index.

KEYWORDS

analgesic, anti-inflammatory, antiulcer, codrug, enzymatic hydrolysis, ketoprofen

1 | INTRODUCTION

Nonsteroidal anti-inflammatory drugs (NSAIDS) belong to one of the most common therapeutically used group of agents in the world for their analgesic, antipyretic, anti-thrombogenic effects other than the anti-inflammatory effect in the management of inflammation and pain in rheumatologic conditions like rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, gout, and musculoskeletal disorders.[1] However, the usefulness of NSAIDs is restricted due to the higher prevalence of gastrointestinal adverse effects including gastric ulceration, perforation, and their associated complications.[2] Both therapeutic and side effects of NSAIDs are dependent on cyclooxygenase (COX) inhibition[3–5] that results in the inhibition of

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prostaglandin (PG) synthesis and the reduced PG levels in GIT results in NSAIDS induced gastropathy as PGs preserve gastric mucosal blood flow, enhance protective mucus, as well as bicarbonate release, inside the gastric milieu.[6,7] Various studies revealed that GI intolerance and poor patient compliance are the major limitations of NSAIDS therapy and, therefore, to design and develop gastric-sparing and gastro-protecting NSAIDS is a hot area of drug research. Since the last two decades, NSAIDs have been altered in varied ways with the aim of designing safe, more effective NSAIDs with reduced GI toxicity.[8] These approaches include:

1. Design of selective COX-2 inhibitors with decreased gastric toxicities[9–11] but there has been an associated risk of potential liver toxicity and cardiovascular complication[12] leading to the withdrawal of some potent COX-2 selective inhibitors.[13]
2. Combining both COX and 5-lipooxygenase (5-LOX) dual inhibitors as it is believed that dual inhibition of both leukotrienes (LTs) and PGs synthesis may lead to enhanced and wider anti-inflammatory activity with less gastric side effects.[14] Results with dual COX/5-LOX inhibitors seem to be promising but large numbers of clinical trials are required to evaluate the safety and efficacy of these agents.[15–17]
3. Design of nitric oxide-releasing NSAIDs,[18,19] which were based on the fact that nitric oxide (NO), is an endogenous gaseous mediator of GI mucosal defences.[20,21] But recent studies indicated the possibility of NO-involvement in the pathogenesis of arthritis and subsequent tissue destruction.
4. Design of prodrugs of NSAIDS in which two different therapeutic agents with corresponding pharmacological properties are combined to produce a single chemical entity (a hybrid). This approach is used to alter the properties of the parent drugs temporarily with the aim of increasing their usefulness and reducing their toxic and unwanted side effects.[17,22] Mutual codrugs of various NSAIDs, such as flurbiprofen,[23] aceclofenac,[24] diclofenac,[25] ibuprofen,[26] and mefenamic acid[27,28] have been successfully synthesized with promising results. Because of the benefits of this approach, various codrugs of NSAIDs have been developed that are being used clinically and available in the market as shown in Figure 1.

Ketoprofen is one of the most effective NSAIDs. Besides, inhibiting PG at the central level, it also activates the serotonergic mechanism and releases 5-hydroxytryptamine (serotonin).[29] Thus, it has superiority over other NSAIDs in treating various neurodegenerative diseases like Alzheimer's and Parkinsonism.[30] Its new role has also been discovered in cancer,[31,32] cardiac,[33] and cerebrovascular[34] diseases. But due to its adverse GI side-effect on long-term use, ketoprofen is not superior to other NSAIDs despite having a dual effect on PGs and LTs.

It has been well documented that the release of reactive oxygen species (ROS) plays a vital role in the forming of gastric mucosal lesions due to NSAIDs therapy.[35] The metabolism of arachidonic acid, platelets, macrophages, and smooth muscles generate ROS that may contribute to gastric mucosal damage. NSAIDs affect a variety of enzyme systems, resulting in an increased ROS concentration within the cell, with irreversible damage to lipids, proteins, nucleoproteins, and DNA.[36] Literature study revealed that antioxidants, such as GSH (glutathione), vitamin E, vitamin C, not only prevent gastric ulceration and lipid peroxidation but also preserve glutathione-type peroxidase (GPO) activity. Hence, it is appropriate to coadminister the NSAIDs and antioxidants in the form of a single chemical entity called codrug in which two different compounds having synergistic therapeutic activity are combined in one molecule. It is suggested that these codrugs having two pharmacologically synergistic properties, anti-inflammatory and antioxidant activity, will result in the development of more efficacious safer NSAIDs[23,24] by masking carboxylic group (–COOH). In view of the fact that the GI-adverse effects of most NSAIDs having a carboxylic group are largely due to local phenomenon/direct irritant action.[37]

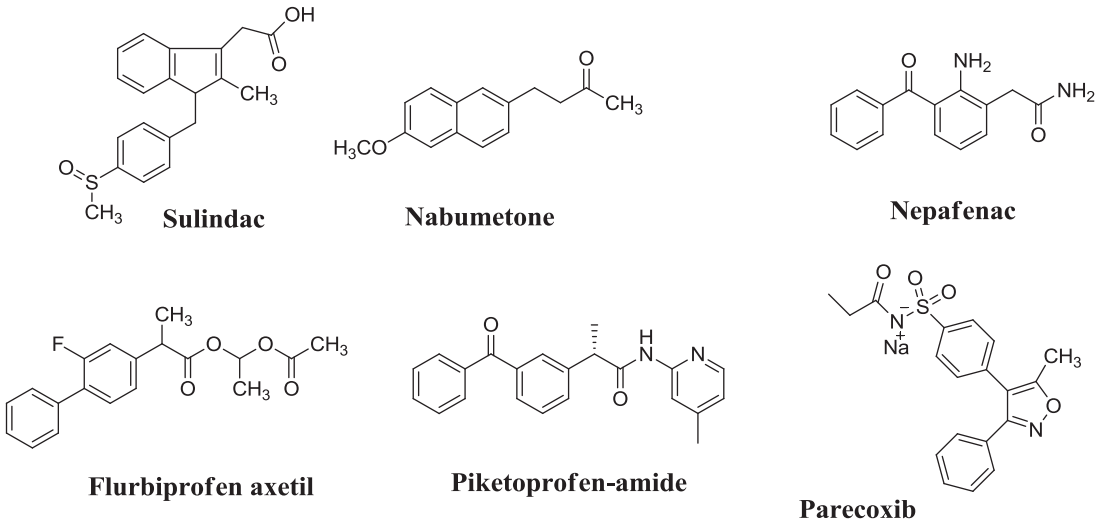


FIGURE 1 List of some clinically available prodrugs of NSAIDs. NSAIDs: nonsteroidal anti-inflammatory drugs

In the present study, we envisage designing various codrugs of ketoprofen by chemical combination with various antioxidants for increasing efficacy and reducing side-effects of ketoprofen. To fulfill the above objectives, we have used various natural antioxidants, such as thymol, guaiacol, eugenol, vanillin, sesamol, curcumin, gallic acid, and the phytoalcohol, including menthol to combine with ketoprofen. Literature studies reveal the analgesics, anticarcinogenic, anti-inflammatory, and antioxidant properties of these natural antioxidants.[38–40] These herbal antioxidants are being used as food additives for ages so they have proven safety.[41] In our previous work, we have found that ketoprofen linked to antioxidants through glycolic spacer showed encouraging results.[42] Hence, in this study, we have designed and synthesized different ester codrugs of ketoprofen with various other antioxidants. It has already been studied that conversion of conventional NSAID to the ester derivatives increases the size of the molecule that causes the molecule to be selective fits into COX-2 active site compared with COX-1 site.[43] This explains their better analgesic and anti-inflammatory activities with reduced GI-toxicities. Based on these facts, various ketoprofen–phytophenols/alcohol ester codrugs were synthesized without spacer (**IIa–h**) and with the glycolic (–OCH_2-COO–) linkage double ester derivatives (**IIIa–h**) as per Scheme 1. Sometimes simple aliphatic/aromatic esters may not be sufficiently labile in vivo.[32] So as to ensure sufficiently high rate and extent of release of parent drug from the codrug, double ester codrug approach is used in which the terminal ester group is sterically less hindered due to the presence of glycolic acid spacer –OCH_2-COO.[25,44,45] All the prepared sixteen codrugs were evaluated for their solubility, lipophilicity, and stability study in different gastric simulated fluids. They were also investigated for their anti-inflammatory, analgesic, antiulcer, and antioxidant properties. These ketoprofen–antioxidant codrugs are likely to be absorbed through the GIT in an inactive form and release the parent ketoprofen and the antioxidant (phytophenols/alcohols) after enzymatic cleavage.

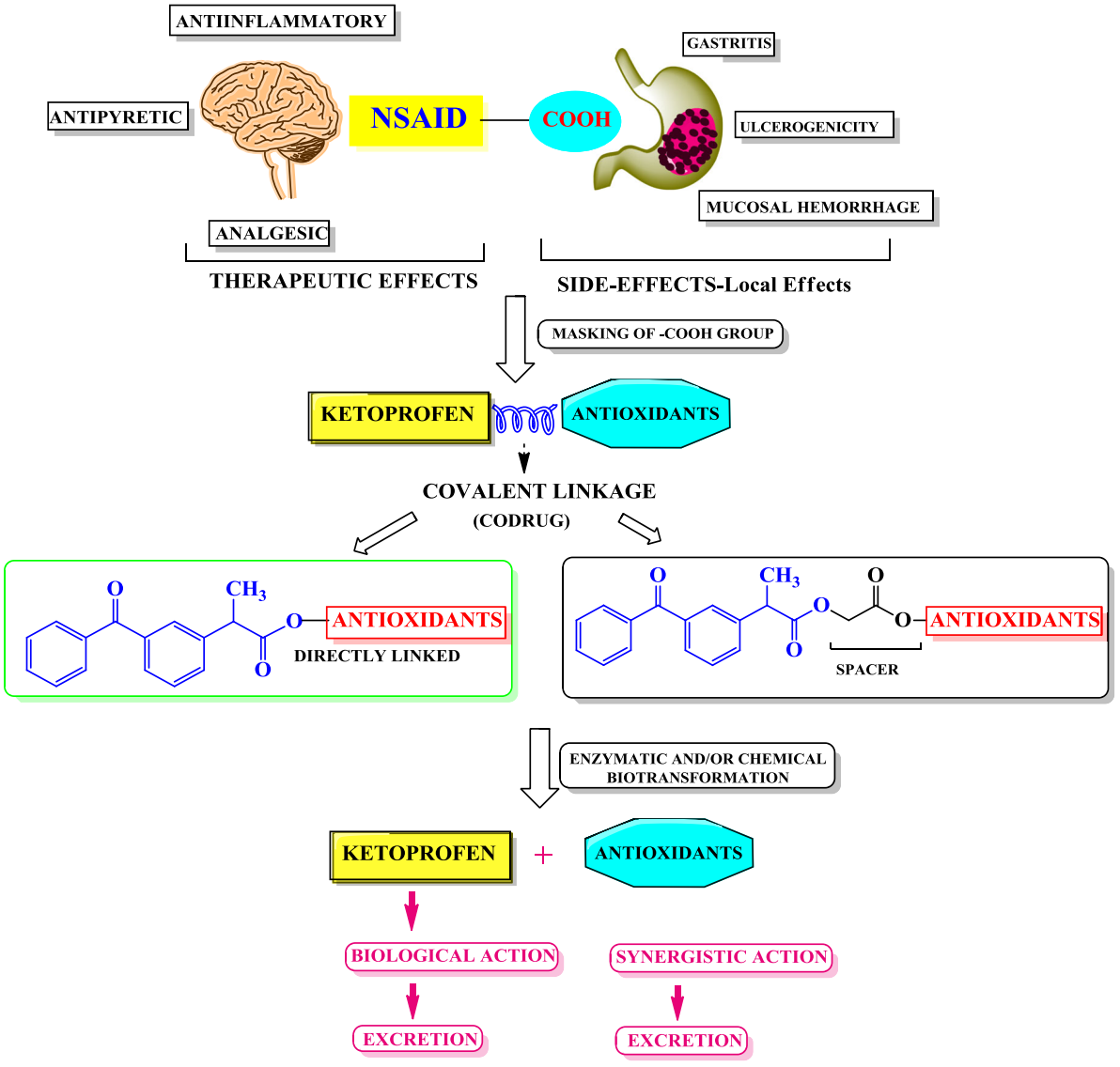
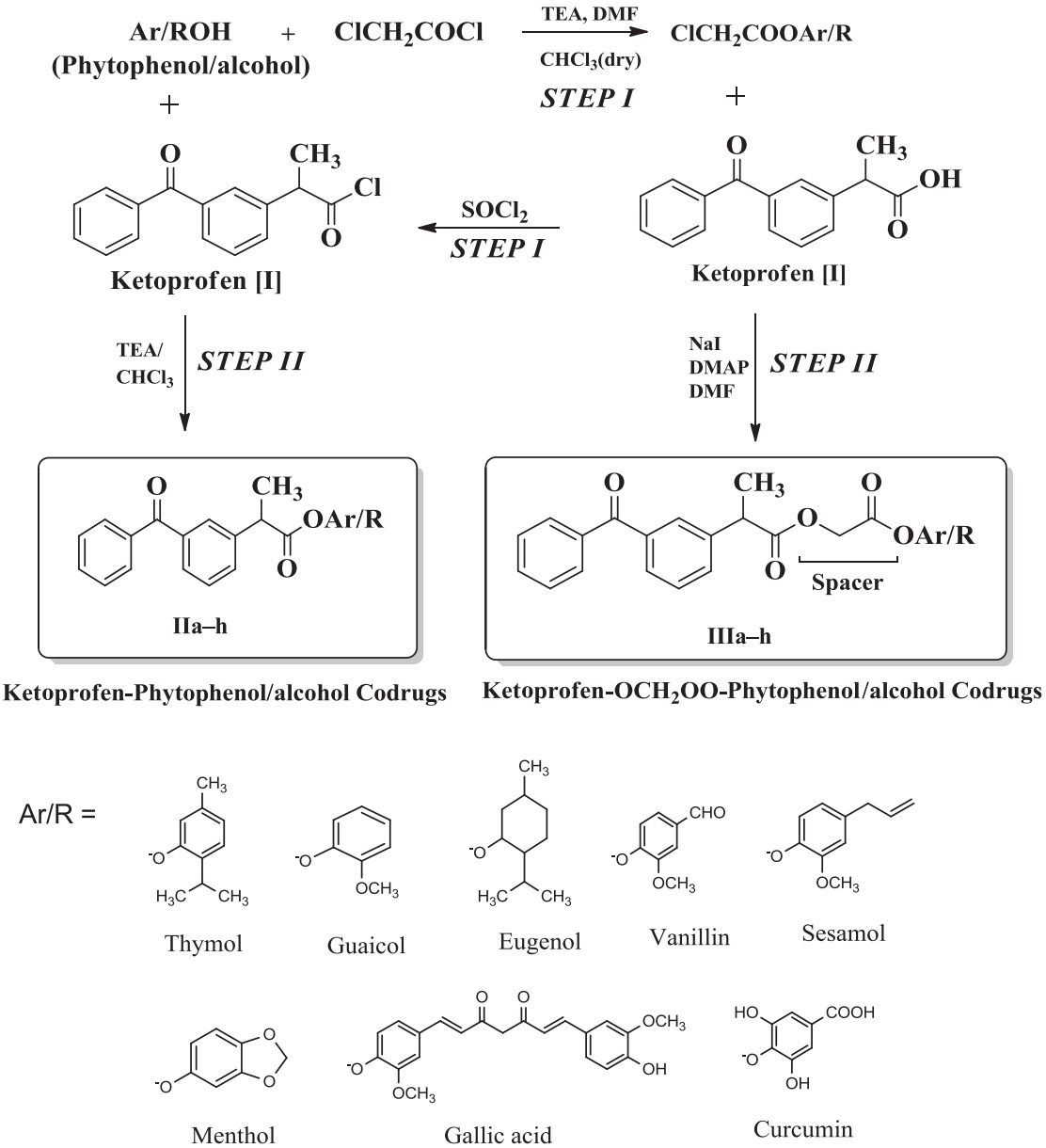


FIGURE 2 Proposed mechanism of codrug activation inside the body



SCHEME 1 Sequence of steps for the synthesis of ketoprofen–antioxidants (**IIa–h**) and ketoprofen–OCH_2COO–antioxidants (**IIIa–h**) mutual codrugs

That may evade gastric side-effects through masking of the carboxylic group of ketoprofen and through the antioxidant properties by quenching ROS (Figure 2).

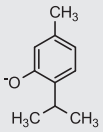
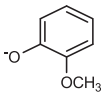
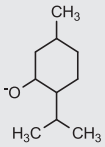
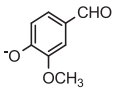
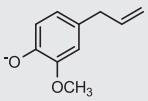
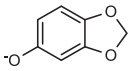
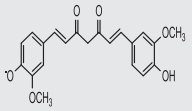
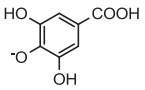
2 | RESULTS AND DISCUSSION

2.1 | Solubility and partition coefficient

The physicochemical properties like solubility and partition coefficient influence the therapeutic efficacy and pharmacokinetic profile of drugs. For codrugs to be bioavailable, they should have optimum solubility and lipophilicity. Therefore, these physicochemical properties have been taken into account while predicting the passive absorption of drugs molecules in vivo.[46] The partition coefficient is the measure of the lipophilicity of the drug. Absorption is increased by high lipophilicity of drugs so the partition coefficient. The solubility of 10 μg/ml drug and a partition coefficient of 100 or more (i.e., log $P > 2$) are found to be optimum for the drugs to be bioavailable effectively after oral administration. Limited solubility (≤1%) in GI fluids resulted in poor GI-absorption. For the lipophilicity measurements, the octanol/water partition coefficient P and log P are used which is calculated as:

$$\text{Partition coefficient } (P) = \frac{\text{Concentration of drug in octanol} \times \text{Dilution factor}}{\text{Concentration of drug in buffer}}$$

TABLE 1 R_f values, % yield, solubility, and log *P* of the ketoprofen–antioxidants codrugs (**IIa–h**)

S. No	Compound	Ar/R	R_f-value	Yield (%)	Solubility (μg/ml) (pH = 7.4)	Log *P*
1	Standard (**I**)	H	0.5	–	51	3.21
2	K-T (**IIa**)		0.45	49.2	5.67	6.38
3	K-G (**IIb**)		0.95	43.4	12.46	4.83
4	K-M (**IIc**)		0.82	38.5	9.86	5.99
5	K-V (**IId**)		0.81	46.5	13.39	4.71
6	K-E (**IIe**)		0.41	51.7	9.68	5.74
7	K-Se (**IIf**)		0.39	45.3	12.05	4.12
8	K-Cu (**IIg**)		0.64	46.2	12.16	5.37
9	K-Ga (**IIh**)		0.90	39.8	11.73	3.28

Ketoprofen has limited solubility so its ester codrugs were prepared and they were found to have a fair solubility in phosphate buffer (pH = 7.4) and greater lipophilicity than ketoprofen. The results for solubility and partition coefficient studies for ketoprofen–OCH_2COO–phytophenols/alcohol are given in Table 1 and Table 2. From the results, it is clear that the prepared ketoprofen codrugs are suitable for oral administration.

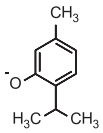
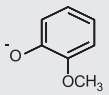
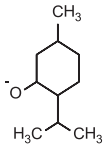
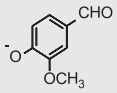
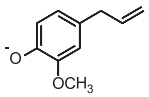
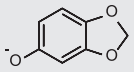
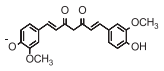
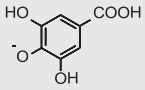
2.2 | Kinetics of hydrolysis studies in SIF and 80% human plasma

It is the crucial requirement of any codrugs/codrugs to remain chemically stable at the undesired site and rapidly undergo enzymatic cleavage at the desired site to release the parent drug. Accordingly, our synthesized codrugs, during their passage through the gastric tract should be chemically stable and should be hydrolyzed to parent drug after absorption in the blood. Therefore, these codrugs were subjected to various in vitro hydrolysis studies to evaluate their stability in simulated gastric fluid and blood plasma. In this study, UV spectrophotometer was used to detect and monitor the hydrolysis of tested codrugs. All the kinetic studies were carried out in triplicate. The *k* values from the plot were calculated separately and the average *k* and standard deviation value was determined. Pseudo-first-order rate constants for the appearance of ketoprofen in different media were determined by linear regression analysis of the plot of log concentration of ketoprofen versus time. The observed rate constant of hydrolysis (K_{obs}) was calculated from the slope of the curve, and the half-life was calculated according to the following equation that derivative from the first order kinetic law: K_{obs} = slope × 2.303 and $t_{1/2} = 0.693/K_{obs}$

The results are collected in Table 3 and Table 4 showing the calculated half-lives for codrugs in different media. It is revealed that these codrugs (**IIa–h**) were chemically stable in pH 7.4 and pH 1.2 with half-lives ranging from 28–44 hr to 74–128 hr, respectively. In the case of ketoprofen–OCH_2COO–phytophenols/alcohol mutual codrugs (**IIIa–h**), the $t_{1/2}$ in phosphate buffer (pH7.4) and pH 1.2 were found to be 35–48 hr and 81–124 hr, respectively. It can be concluded that the synthesized codrugs are relatively stable in pH 1.2 and 7.4 and, hence, suitable for oral administration.

The rate constants and $t_{1/2}$ for ketoprofen–phytophenols/alcohol mutual codrugs in plasma (80%, pH 7.4) were found in the

TABLE 2 R_f values, % yield, solubility, and log *P* of the ketoprofen–OCH_2COO–antioxidants (**IIIa–h**) mutual codrugs

S. No	Compound	Ar/R	R_f-value	Yield (%)	Solubility (μg/ml) (pH = 7.4)	Log *P*
1.	KTS (**IIIa**)		0.63	56.4	5.06	6.09
2.	KGS (**IIIb**)		0.54	48.3	10.37	4.23
3.	KMS (**IIIc**)		0.79	42.6	7.81	5.76
4.	KVS (**IIId**)		0.72	52.5	12.52	4.21
5.	KES (**IIIe**)		0.63	48.9	7.89	5.16
6.	KSeS (**IIIf**)		0.41	54.1	10.17	4.39
7.	KCuS (**IIIg**)		0.39	42.8	8.94	5.67
8.	KGaS (**IIIh**)		0.51	43.7	9.25	3.35

Note. KCuS: ketoprofen–curcumin with spacer; KES: ketoprofen–eugenol with spacer; KGaS: ketoprofen–gallic acid with spacer; KGS: ketoprofen–guaiacol with spacer; KMS: ketoprofen–menthol with spacer; KSeS: ketoprofen–sesamol with spacer; KTS: ketoprofen–thymol with spacer; KVS: ketoprofen–vanillin with spacer.

range of 0.367–0.537 hr^{-1} and 21.99–32.23 hr, respectively. The result suggests that the mutual codrugs are readily hydrolyzed in plasma to release the parent NSAID. In comparison to the rate of hydrolysis in SGF (pH 1.2) and hydrolysis in SIF (pH 7.4), the rate of hydrolysis in plasma is faster showing that the enzymatic reactivities of codrugs are greater than their respective pH reactivity.

2.3 | Biological evaluation/ pharmacological studies

The ketoprofen was combined with the natural antioxidants to design codrugs in the hope to develop novel molecules having improved anti-inflammatory and analgesic activity and devoid of gastric side-effects. Hence, these codrugs were evaluated for anti-inflammatory,

TABLE 3 In vitro hydrolysis/chemical stability rates of ketoprofen–phytophenols/alcohol mutual codrugs (**IIa–h**)

Compound	$K_{pH7.4}$ (hr^{-1}) × 10^{-3}	$T_{1/2(pH7.4)}$ (hr)	$K_{pH1.2}$ (hr^{-1}) × 10^{-4}	$T_{1/2(pH1.2)}$ (hr)	K_{Plasma} (hr^{-1})	$T_{1/2Plasma}$ (min)
KT (**IIa**)	1.73	400.58	5.9	1174.58	1.17	35.54
KG (**IIb**)	1.82	380.77	5.0	1386.00	1.13	36.80
KM (**IIc**)	3.43	202.04	6.1	1136.06	1.29	32.23
KV (**IId**)	1.86	372.58	6.4	1082.82	1.25	33.26
KE (**IIe**)	1.97	351.78	6.2	1117.74	1.36	30.57
KSe (**IIf**)	1.79	387.15	6.8	1019.12	1.33	31.26
KCu (**IIg**)	1.58	441.40	7.3	949.32	1.27	32.74
KGa (**IIh**)	1.97	351.77	7.9	877.21	1.47	37.13

Note. KCu: ketoprofen–curcumin; KE: ketoprofen–eugenol; KGa: ketoprofen–gallic acid; KG: ketoprofen–guaiacol; KM: ketoprofen–menthol; KSe: ketoprofen–sesamol; KT: ketoprofen–thymol; KV: ketoprofen–vanillin.

TABLE 4 In vitro hydrolysis/chemical stability rates of ketoprofen–OCH_2COO-phytophenols/alcohol mutual codrugs (**IIIa–h**)

Compound	$K_{pH7.4}$ (hr^{-1}) × 10^{-3}	$T_{1/2(pH7.4)}$	$K_{pH1.2}$ (hr^{-1}) × 10^{-4}	$T_{1/2(pH1.2)}$	K_{Plasma} (hr^{-1})	$T_{1/2Plasma}$ (min)
KTS (**IIIa**)	1.92	360.94	6.1	1136.07	1.47	28.28
KGS (**IIIb**)	1.64	422.56	5.7	1215.79	1.39	29.91
KMS (**IIIc**)	2.84	244.01	11.6	597.41	1.71	24.32
KVS (**IIId**)	1.94	357.22	6.9	1004.35	1.38	30.13
KES (**IIIe**)	2.43	285.18	8.5	815.29	1.69	24.6
KSeS (**IIIf**)	1.89	366.67	7.1	976.06	1.44	28.88
KCuS (**IIIg**)	1.83	378.69	7.6	911.84	1.63	25.51
KGaS (**IIIh**)	2.16	320.83	8.1	855.56	1.41	29.49

Note. KCuS: ketoprofen–curcumin with spacer; KES: ketoprofen–eugenol with spacer; KGaS: ketoprofen–gallic acid with spacer; KGS: ketoprofen–guaiacol with spacer; KMS: ketoprofen–menthol with spacer; KSeS: ketoprofen–sesamol with spacer; KTS: ketoprofen–thymol with spacer; KVS: ketoprofen–vanillin with spacer.

analgesic and GI-ulceration properties. Institutional Animal Ethics Committee approves the experimental protocol and written permission has been taken from the in-house ethics committee (CPCSEA/SCOP/2017/IAEC/10/02) to complete this study.

2.3.1 | Anti-inflammatory activity

Tissue damage by infection, inflammation, trauma, etc. results in increased production of various inflammatory mediators like PGs, LTs, cytokines, ROS, etc. When the pro-oxidant conditions dominate either due to increased generation of the free radicals or due to poor scavenging of the free radicals due to deficiency of endogenous or dietary antioxidants, then it leads to tissue injury and subsequent diseases. Although oxidative stress is a secondary event to many inflammatory reactions it plays an important role in furthering the tissue injury. Hence, the concomitant administration of an antioxidant with an NSAID increases their anti-inflammatory action.[47–49] The results of left hind paw edema test for the codrugs with the spacer and without spacer are as given in Table 5. The codrugs K-V, K-E, K-Se, K-Cu, and K-Ga showed increased anti-inflammatory activity to the standard (ketoprofen). This may be due to the antioxidant activity of the phytophenolic promoiety. The codrugs K-V and K-G showed comparable activity to that of the standard (ketoprofen) and the codrugs K-M and K-T showed significantly lesser activity as compared to standard (ketoprofen) that may be due to the lower antioxidant profile of menthol/thymol promoieties, respectively. The mutual codrugs of ketoprofen–phytophenols/alcohol with the $-CH_2COO-$ spacer (KTS, KGS, KMS, KVS, KES, KSeS, KCuS, and KGaS) have been evaluated for their anti-inflammatory activity at equimolar doses to ketoprofen (20 mg/kg). KES, KSeS, KCuS, and KGaS showed a significant increase in anti-inflammatory activity. KVS and KGS showed a lesser increase in activity, whereas KMS and KTS showed comparable activity than ketoprofen. This increased activity may be due to the antioxidant profile of their promoiety. The introduction of $-OCH_2COO-$ spacer showed an increase in activity compared with the activity of simple ester codrugs without the spacer. This may be due to better release profile of spacer codrugs in human plasma, as shown by stability studies data.

2.3.2 | Analgesic activity

Ketoprofen shows major inhibition in writhing at 20 mg/kg dose. The results are shown in Table 5. Lower analgesic activities are shown by codrugs K-T and K-M in equimolar doses. The codrug K-G showed a similar analgesic effect to that of parent NSAID ketoprofen. The other codrugs (K-E, K-V, K-Se, KCu, and KGa) showed significant analgesic activity than that of the standard (ketoprofen). In the results of with glycolic ($-CH_2COO$) spacer codrug derivatives the codrugs KTS, KMS, KGS, KVS, and KES showed lesser analgesic activity than that of the parent NSAID, ketoprofen. But the codrugs KSeS, KCuS, and KGaS showed analgesic activity comparable to that of ketoprofen.

2.3.3 | Antiulcer/gastrointestinal erosion assay

The results showed that there is a significant reduction in the ulcer index as compared with the parent NSAID, ketoprofen (Table 6, Table 7). There is a marked decrease in ulcer index of the codrugs (for both with the spacer and without spacer derivatives). The codrugs K-Se, K-Cu, and K-Ga showed the maximum decrease in ulcer index whereas the codrugs derivatives with thymol and menthol showed lesser antiulcer activity as compared with the derivatives with sesamol, eugenol, vanillin, curcumin, and with gallic acid. The antiulcer activity of these test compounds are directly related to their respective antioxidant potential. KTS and KMS showed lesser antiulcer activity (higher ulcer index 2.64 and 2.93) as compared with KGS, KCuS, KGaS, KGS, and KSeS (antioxidant potential). This significantly reduced ulcer index may be due to the combined effect of antioxidant properties of the promoieties and masking of the free carboxylic group of the parent NSAID (combined synergistic effects).

2.3.4 | Antioxidant studies (in vitro)

In addition to NSAIDs induced GI-pathogenesis due to PG inhibition (PG induce the synthesis of protective mucus), generation of ROS (reactive oxygen species) also plays an important role in the

TABLE 5 Anti-inflammatory and analgesic effect studies of ketoprofen–antioxidants **(IIa–h)** and ketoprofen–OCH_2COO–antioxidants **(IIIa–h)** mutual codrugs of ketoprofen

S. NO	Treatment		% Increase in Paw volume mean ± *S.E.M* (2 hr)	% Increase in Paw volume mean± *S.E.M* (4 hr)	% Inhibition in writhings ± *S.E.M*
1.	Control (cmc)	0.5%	49.65 ± 1.36	69.05 ± 1.28*	–
2.	Standard (ketoprofen) *Without spacer prodrugs*	20	24.38 ± 1.87*	29.53 ± 0.92	71.59 ± 1.25
3.	K-T (ketoprofen–thymol prodrug)	30.38	24.17 ±1.54**	29.52 ± 1.42**	67.46 + 1.47***
4.	K-G (ketoprofen–guaiacol prodrug)	28.33	21.91 ± 0.61**	24.54 ± 1.07**	69.01 ± 1.03***
5.	K-M (ketoprofen–menthol prodrug)	30.85	29.65 ± 1.20**	32.71 ± 1.46**	66.12 ± 0.73***
6.	K-V (ketoprofen–vanillin prodrug)	30.54	21.61 ± 1.32**	23.68 ± 0.78**	68.94 + 1.32***
7.	K-E (ketoprofen–eugenol prodrug)	31.48	19.46 ± 0.68**	20.14 ± 1.01**	69.43 ± 1.16***
8.	K-Se (ketoprofen–sesamol prodrug)	29.43	18.50 ± 0.76**	20.57 ± 1.49**	70.89 ± 1.49***
9.	K-Cu (ketoprofen–gurcumin prodrug)	47.53	18.15 ± 1.74**	18.46 ± 0.94**	72.65 ± 0. 92***
10.	K-Ga (ketoprofen-gallic acid prodrug) *With spacer prodrugs*	33.49	17.68± 1.14**	19.35 ± 1.08**	70.37 ± 1.40***
11.	KTS (ketoprofen-OCH_2COO-thymol prodrug)	34.94	23.43 ± 0.89	28.79 ± 1.14	71.19 ± 1.41***
12.	KGS (ketoprofen-OCH_2COO-guaiacol prodrug)	32.90	19.25± 1.18**	22.66 ± 1.58**	75.46 ± 1.26***
13.	KMS (ketoprofen–OCH_2COO-menthol prodrug)	35.42	24.92 ± 1.37***	27.61 ± 1.46***	69.44 ± 1.36***
14.	KVS (ketoprofen-OCH_2CO–vanillin prodrug)	35.10	20.13 ± 0.65**	21.94 ± 1.78**	70.14 ± 1.13***
15.	KES (ketoprofen–OCH_2COO-eugenol prodrugl)	36.04	17.45 ± 1.26**	19.06 ± 0.82**	81.54 ± 1.28***
16.	KSeS (ketoprofen–OCH_2COO-sesamol prodrug)	33.49	16.87 + 1.48**	17.38 ± 0.49**	80.98 + 1.74***
17.	KCuS (ketoprofen–OCH_2COO-curcumin prodrug)	52.09	15.76 ± 0.17**	16.43 ± 0.61**	79.06 ± 0.08***
18.	KGaS (ketoprofen–OCH_2COO-gallic acid prodrug)	36.52	16.54 ± 1.92**	17.43 ± 1.21**	78.11 ± 1.40***

*$p < 0.05$ as compared to control.
**$p < 0.05$ as compared to standard.
***$p < 0.05$ as compared to standard (ketoprofen 20 mg/kg, p.o).

TABLE 6 Grades for the observed lesions

Grades	Lesions
[0]	Normal colored stomach
[0.5]	Red coloration
[1.0]	Spot ulcers
[1.5]	Hemorrhagic streaks
[2.0]	Ulcer >3 but <5
[3.0]	Ulcers >5

TABLE 8 % DPPH radical scavenging

Compounds	% Scavenging (DPPH*)
Guaiacol	47.10 ± 2.16
Eugenol	79.55 ± 2.45
Vanillin	6.59 ± 1.52
Menthol	5.23 ± 0.06
Sesamol	46 ± 2.36
Thymol	14.77 ± 1.01
GA	70.45 ± 0.09
Curcumin	46.48 ± 1.12
Vit. C (standard)	94.27 ± 1.67

*$p < 0.05$ as compared to control.

pathogenesis of GI ulceration, which is proven by various studies. The ester codrugs of NSAIDs with phytophenols/alcohol are prepared with the aim to have an antioxidant action of phytophenols/alcohol to counteract this side effect of NSAIDs. Antioxidant studies (in vitro) were done (Table 8) to find out whether the prepared codrugs possess antioxidant properties. Among the antioxidants tested, eugenol and gallic acid have antioxidant activity compared with vitamin C, whereas guaiacol and curcumin have lesser antioxidant activity but better activity than menthol, vanillin, and thymol.

3 | CONCLUSION

The synthesis of various mutual codrugs of ketoprofen–antioxidant has been done by using those naturally occurring phytophenols/alcohols that have proven therapeutic utility in various inflammatory conditions. It has been observed that codrugs synthesized were of optimum physicochemical properties like solubility and partition coefficient, suggesting their improved bioavailability. The absence of gastric damage in all the cases of codrug derivatives (with and without spacer) may be due to the combined effect of the antioxidant activity of the phytophenols/alcohol promoieties as well as the masking of the –COOH group of the NSAID. It has been concluded that there is a definite advantage of administering these codrugs for the treatment of chronic inflammatory disorders like rheumatoid arthritis, osteoarthritis, Alzheimer's disease, cancer, etc. Further, the introduction of $-OCH_2COO-$ spacer did not show a significant increase in the activity but retained the activity of the parent ketoprofen with reduced gastric side-effects. They showed better activity than that of respective simple ester (without spacer) codrugs.

TABLE 7 Acute antiulcer/gastrointestinal erosion assay (GIER) studies of ketoprofen–antioxidants (**IIa–h**) and ketoprofen–OCH_2COO–antioxidants (**IIIa–h**) mutual codrugs of ketoprofen

S.NO.	Treatment	Molar equivalent dose mg/kg, p.o.	Ulcer index mean ± EM
1	Control	0.5%	0.18 ± 0.06
2	Standard (ketoprofen) *Without spacer prodrugs*	80	4.27 ± 0.63*
3	K-G (ketoprofen-guaiacol prodrug)	121.52	1.88 ± 0.54**
4	K-V (ketoprofen–vanillin prodrug)	122.16	1.57 ± 0.63**
5	K-E (ketoprofen–eugenol prodrug)	125.92	1.98 ± 0.84**
6	K-Se (ketoprofen–sesamol prodrug)	117.72	1.76 ± 0.39**
7	K-Cu (ketoprofen–curcumin prodrug)	190.12	1.17 ± 0.28**
8	K-Ga (ketoprofen–gallic acid prodrug)	133.96	1.58± 0.12**
	With spacer prodrugs		
9	KTS (ketoprofen-OCH_2COO-thymol prodrug)	139.76	2.64 ± 0.21**
10	KVS (ketoprofen-OCH_2COO-vanillin prodrug)	140.40	1.24 ± 0.39**
11	KES (ketoprofen-OCH_2COO-eugenol prodrug)	144.16	1.63 ± 0.15**
12	KMS (ketoprofen-OCH_2COO-menthol prodrug)	141.16	2.93 ± 0.41**
13	KCuS (ketoprofen-OCH_2COO-curcumin prodrug)	208.36	0.95 ± 0.33**
14	KSeS (ketoprofen-OCH_2COO-sesamol prodrug)	133.96	0.96 ± 0.51**
15	KGaS (ketoprofen-OCH_2COO-gallic acid prodrug)	146.08	1.03 ± 0.25**
16	KGS (ketoprofen-OCH_2COO-guaiacol prodrug)	131.6**	1.73 ± 0.46**

*$p < 0.05$ as compared to control.
**$p < 0.05$ as compared to standard.

In conclusion, the results are promising and indicate that these codrugs showed the retention of anti-inflammatory and analgesic activity with a significant reduction in ulcer index. Still, we hope that the outcome of this study endows with an indispensable knowledge base for the prospective design of novel safer NSAIDs.

4 | EXPERIMENTAL

4.1 | Chemistry

4.1.1 | General

Ketoprofen was obtained from Infinity Laboratories Pvt. Ltd., Derabassi. All the phytoalcohols/phenols were purchased from S.D. Fine Chemicals Ltd. and from Loba Chemie. The melting points were determined on Veego melting point apparatus 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 as an internal standard. Infrared (IR) spectra were obtained with Perkin Elmer 882 spectrometer and RXI, FT-IR model using KBr-pellets.The TOF-MS-ES^{+} spectra of the compounds were recorded on Waters micromass Q-TOF mass spectrometer. Elemental analyses were carried out on a Perkin–Elmer 2400 CHNS/O elemental analyzer. TLC plates were prepared with silica gel G (60–120 mesh, BDH) and activated at 110°C for 30 min and analyzed with iodine vapors for monitoring of reactions and to check the homogeneity of products. All the solvents were dried and freshly distilled before use, according to standard procedure.

The InChI codes of the investigated compounds together with some biological activity data are provided as Supporting Information.

4.1.2 | General procedure for preparation of ketoprofen–antioxidants ester codrugs without spacer (IIa–h)

Step I: Synthesis of ketoprofen chloride

Ketoprofen (0.504 g, 2 mmol) and few drops of DMF were dissolved in dry benzene in the round bottom flask and stirred for 15 min inside an ice bath at 0°C. Then, a slight excess of freshly distilled in thionyl chloride (0.7 ml, 10 mmol) was added dropwise over 15–20 min. Stirring was continued at room temperature for 8 hr. After completion of the reaction, the excess of thionyl chloride was removed by distillation under reduced pressure to obtain a yellow semi-solid which was used in next step without further purification.

Step II: Synthesis of ketoprofen–phytoalcohol/phenols ester

A mixture of respective phytoalcohol/phenols (2 mmol), triethylamine (TEA) (0.7 ml, 10 mmol) and dry chloroform (25 ml) was stirred in ice-salt mixture at −10°C. To this reaction mixture, a solution of ketoprofen chloride (2 mmol) in dry chloroform (25 ml) was added dropwise with constant stirring at −10°C for 1 hr and then kept at room temperature overnight. After completion of the reaction, indicated by TLC, chloroform layer was washed with 1 M sodium carbonate solution (3 × 25 ml), distilled water (3 × 25 ml), HCl (5%, 3 × 50 ml), NaOH (5%, 3 × 50 ml), and finally with brine solution (2 × 50 ml) and dried over sodium sulfate to get gummy residue. Then the product was purified by column chromatography with gradient elution with methanol in chloroform (up to 10%) using silica gel (80–120 mesh), to obtain the final product (**IIa–h**) (Table 1).

4.1.3 | Chemical characterization of the synthesized codrugs-antioxidant codrugs without a spacer (IIa–h)

Ketoprofen, 2-(3-benzoylphenyl)propanoic acid (I)

IR (KBr, ν_{max}, cm^{-1}): 3054 (OH, -COOH), 2995–3000 (CH, Ar), 2880 (CH), 1655, 1697 (C=O), 1420, 1445 (C-C), 1285 (C-O), 966 (O-H), 716 (CH "oop" Ar). ^{1}H-NMR ($CDCl_3$): δ 11 (1H, s, -COOH), 7.5–7.8 (9 H, m, ArH), 3.9–4.3 (1H, q, ArH), 1.6 (3H,d, CH_3). ^{13}C-NMR (in ppm): 14 (CH_3CH), 426 ($CHCH_3$), 130–135 (ArCs), 142 (ArC=OAr).

Ketoprofen–thymol (K-T), 2-isopropyl-5-methylphenyl-2-(3-benzoylphenyl)propanoate (IIa)

IR (KBr, ν_{max}, cm^{-1}): 2990, 2985 (C-H), 1736 (C=O ester), 1650 (C=O ketone), 1457 (Ar C=C), 1371 ($CH(CH_3)_2$) 1231 (C-O-C asym.), 1043 (C-O-C sym.), 935, 847 (C-H Ar). ^{1}H-NMR ($CDCl_3$): δ 7.7–7.8 (3H, m, ArH), 7.6 (1H, dt, ArH), 6.0–7.6 (2H, m, ArH), 7.4–7.5 (3H, m, ArH), 6.6–6.7 (3H, m, ArH - thymol), 1.27–1.29 (6H, d, $CH(CH_3)_2$ - thymol), 1.53–1.55 (3H, s, CH-CH_3), 2.30 (3H, s, Ar-CH_3), 2.90–2.95 (1H, m, $CH(CH_3)_2$ - thymol), 3.79–3.86 (1H, q, $CHCH_3$), 4.73–4.90 (2H, q, O-CH_2-COO). ^{13}C-NMR (in ppm): 21.2 (Ar-CH_3), 23.4 (CH-CH_3), 27.6 ($CH(CH_3)_2$ - thymol), 122–133 (Ar-Cs), 176.4 (CH_3CHC=O), 197.5 (ArC=OAr). MS (ESI): *m/z* 387 (M+H)$^{+}$. Anal. calcd. for $C_{28}H_{28}O_5$: C, 75.65; H, 6.35 Found: C, 75.45; H, 6.48.

Ketoprofen–guaiacol (K-G), 2-methoxyphenyl-2-(3-benzoyl-phenyl)propanoate (IIb)

IR (KBr, ν_{max}, cm^{-1}): 2952 (aromatic C-H), 1735 (C=O esters), 1658 (C=O ketone), 1281 (C-O ester), 1207, 1165 (Ar-OCH_3), 950, 850, 704 (C-H Ar). ^{1}H-NMR (in $CDCl_3$): δ: 7.26–7.81 (13H, m, Ar-H), 3.82 (1H, q, CH-CH_3), 3.80 (3H, d, $CHCH_3$), 3.68 (3H, s, O-CH_3). ^{13}C-NMR (in ppm): 19.4 (CH-CH_3), 45.1 ($ArCHCH_3$), 52.0 (Ar-OCH_3), 128–141 (Ar-C), 150.9 (Ar-C-OCH_3), 175.2 (–C=O(OAr), 197.3 (Ar-**C**O-Ar). MS (ESI): *m/z* 360 (M^{+}). Anal. calcd. for $C_{28}H_{22}O_6$: C, 71.76; H, 5.30 Found: C, 71.88; H, 5.18.

Ketoprofen–menthol (K-M), 2-isopropyl-5-methylcyclohexyl-2-(3-benzoylphenyl)propanoate (IIf)

IR (KBr, ν_{max}, cm^{-1}): 2986 (ar-C-H), 2954 (aliph. C-H), 1726 (C=O ester), 1650 (C=O), 1457 (C=C), 1371 (CH $(CH_3)_2$), 1232 and 1033 (C-O-C) 937–730 (Ar-C-H). ^{1}H-NMR ($CDCl_3$): δ 7.7–7.8 (3H, m, Ar-H), 7.6 (1H, dt, Ar-H), 7.5–7.6 (2H, m, Ar-H), 7.4–7.5 (3H, m, Ar-H), 4.6–4.7 (1H, m, CH-O), 3.9–4.0 (1H, q, $CHCH_3$), 1.6–1.9 (3H, d, $CHCH_3$), 0.9–1.0 (3H, d, CH_3-menthol), 1.6–1.7 (6H, d, $CH(CH_3)_2$), 0.9–1.1 (4H, m, CH_2-menthol), 1.4–1.5 (2H, m, CH_2-menthol), 1.8–1.7 (1H, m, $CH(CH_3)_2$), 3.9 (1H, m, O-CH-menthol). ^{3}C-NMR (in ppm): 15.9 (CH-CH_3-menthol), 18.5 ($CHCH_3$-ketoprofen), 21.2–22.1 $CH(CH_3)_2$, 23.1 (CH_2 menthol), 26.3 $CH(CH_3)_2$,

35.0 (CH_2-menthol), 47.2 (CH-menthol), 75.4 (COO-C), 130–141 (Ar-Cs), 174.0 (COO), 194.2 (ArC=OAr). MS (ESI): *m/z* 393 (M^+). Anal. calcd. for $C_{28}H_{34}O_5$: C, 74.64; H, 7.61 Found: C, 74. 55; H, 7.50.

Ketoprofen–vanillin (K-V), 4-formyl-2-methoxyphenyl-2-(3-benzoylphenyl)propanoate (IId)

IR (KBr, ν_{max}, cm^{-1}): 3003 (Ar C-H), 1762 (C=O ester), 1697 (C=O aldehyde), 1650 (C=O ketone), 1497 (C=C), 1235 and 1044 (–OCH_3), 1232 and 1042 (C-O), 937, 748 (Ar C-H). ^{1}H-NMR ($CDCl_3$): δ 9.9 (1H, s, CHO) 7.1–7.9 (12H, m, Ar-H), 4.1–4.2 (1H, q, $CHCH_3$), 1.67–1.69 (3H, d, $CHCH_3$), 3.9–4.0 (3H, s, Ar-OCH_3). ^{13}C-NMR (in ppm): 18.6 (CH-CH_3), 45.3 ($CHCH_3$), 56 (Ar-OCH_3), 123–138 (Ar-Cs), 140 (ArC-C=O), 145 (ArC-OC=O), 152 (Ar-C-OCH_3), 172 (CH_3CHC=O), 191 (CHO), 197 (ArC=OAr). MS (ESI): *m/z* 388 (M^+). Anal. calcd. for $C_{26}H_{22}O_7$: C, 69.95; H, 4.97 Found: C, 69.76; H, 4.85.

Ketoprofen–eugenol (K-E), 4-allyl-2-methoxyphenyl-2-(3-benzoylphenyl) propanoate (IIc)

IR (KBr, ν_{max}, cm^{-1}): 3469 (C=C-H), 2984 (ArC-H), 2936 (aliph. C-H), 1737 (C=O esters), 1662 (C=O ketone), 1453 (Ar-C=C), 1233 (C-O ester), 1044 and 1235 (C-H Ar –OCH_3). ^{1}H-NMR ($CDCl_3$) δ: 6.7–7.8 (12H, m, Ar-H), 6.7 (1H, m, CH_2CH=CH_2), 5.0–5.1 (2H, m, CH_2CH=CH_2), 4.06–4.08 (1H, q, CH-CH_3), 3.6–3.7 (2H, d, Ar-CH_2CH=CH_2), 3.3–3.4 (3H, s, Ar-OCH_3), 1.6–1.7 (3H, d, CH-CH_3). ^{13}C-NMR (in ppm): 18.7 (CH-CH_3), 40.0 (Ar-CH_2), 45.3 (CH-CH_3), 55.7 (Ar-OC H_3), 116.1 (CH=CH_2), 138.0 (CH_2CH=CH_2), 112.7–140.6 (Ar-Cs), 150.8 (Ar-C-OCH_3), 172 (-C=O (OAr)), 197 (Ar-C=O Ar). MS (ESI): *m/z* 400 (M^+). Anal. calcd. for $C_{26}H_{24}O_4$: C, 77.98; H, 6.04 Found: C, 77.75; H, 5.88.

Ketoprofen–sesamol (K-Se), benzo[*d*][1, 3]dioxol-5-yl-2-(3-benzoylphenyl)propanoate (IIe)

IR (KBr, ν_{max}, cm^{-1}): 3026 (ArC-H), 2847 (Ar-O-CH_3), 1758 (C=O ester), 1668 (C=O ketone), 1497.56 (C=C Ar), 1249 and 1042 (C-O-C), 936–730 (Ar-C-H). ^{1}H-NMR ($CDCl_3$): δ 6.97–7.83 (12H, m, ArH), 3.78–3.96 (1H, q, $CHCH_3$), 1.69–1.71 (3H, d, $CHCH_3$), 5.92–6.09 (2H, s, CH_2 sesamol). ^{13}C-NMR (in ppm): 13.9 ($CHCH_3$), 40.8 (CH-CH_3), 101.2 (OCH_2O sesamol), 128.6–1498.2 (Ar-Cs), 171.46 (HC-C=O(OAr)), 190.52 (ArC=OAr). MS (ESI): *m/z* 374 (M^+). Anal. calcd. for $C_{23}H_{18}O_5$: C, 73.79; H, 4.85 Found: C, 73.65; H, 4.65.

Ketoprofen–curcumin (K-Cu), [2-(4-((1*E*,6*E*)-7-(4-hydroxy-3-methoxyphenyl)]-3,5-dioxohepta-1,6-dien-1yl)-2-methoxyphenyl-2-(3-benzoylphenyl)propanoate (IIh)

IR (KBr, ν_{max}, cm^{-1}): 3081 (Ar -C-H), 2985 (aliph. -C-H), 2848 (Ar-O-CH_3), 1647 (C=O ketone), 1739 (C=O ester), 1486 (C=C), 1235, 1044 (-OCH_3), 1232 and 1042 (C-O), 936–730 (Ar-C-H bend). ^{1}H-NMR ($CDCl_3$): δ 7.8–6.8 (15H, m, Ar-H), 7.60 (2H, s, CH=CH-Ar), 6.9 (2H, s, O=C-CH=CH-Ar), 6.2–5.4 (1H, s, phenolic-OH), 4.6–4.5 (2H, s, O=C-CH_2C=O), 3.9–3.5 (6H, s, Ar-OCH_3 curcumin), 3.5 (1H, q, $CHCH_3$), 1.6–1.4 (3H, d, $CHCH_3$). ^{13}C-NMR (ppm): 13.9 ($CHCH_3$), 40.1 (CH-CH_3), 115.2–157.9 (Ar-C), 174.2 (HC-C=O(O-Ar)), 57.1 (Ar-O-CH_3), 61.0 (C=OCH_2C=O), 130.0 (Ar-CH=$CHCH_2$), 143.0 (Ar-CH=CH-CH_3), 144.2 (Ar-C-OH), 150 (ArC-OCH_3), 173.0 (-COO-), 200.4 (-C(=O)-C (=O)-). MS (ESI): *m/z* 604 (M^+). Anal. calcd. for $C_{37}H_{32}O_8$: C, 73.50; H, 5.33 Found: C, 73.72; H, 5.65.

Ketoprofen–gallic acid (K-Ga), 4-(2-(3-benzoylphenyl]propanoyl)oxy)-3,5-dihyroxybenzoic acid (IIg)

IR (KBr, ν_{max}, cm^{-1}): 2450–3245 (COOH), 3475 (OH-phenolic), 3327 (-COOH), 2936 (C-H Ar), 1718 (C=O ester), 1232 and 1042 (C-O ester), 1647 (C=O ketone), 1660 (C=C), 813–730 (Ar-C-H). ^{1}H-NMR ($CDCl_3$): δ 9.97 (1H, -COOH gallic acid), 7.26–7.81 (11H, m, Ar-H), 6.99 (2H, s, phenolic-OH), 3.81 (1H, q, $CHCH_3$), 3.68 (3H, d, $CHCH_3$). ^{13}C-NMR ($CDCl_3$, ppm): 18.6 ($CHCH_3$), 44.3 (CH-CH_3), 128.4–138 (Ar-Cs), 141 (COO-C), 175 (HC-C=O (OAr) and (-COOH), 197 (ArC=OAr). MS (ESI): *m/z* 406 (M^+). Anal. calcd. for $C_{23}H_{18}O_7$: C, 67.98; H, 4.46 Found: C, 67.75; H, 4.36.

4.1.4 | Preparation of the ketoprofen–antioxidants ester codrugs with glycolic spacer (IIIa–h)

The general methods for the synthesis of ketoprofen and phytoalcohol/phenols with the glycolic acid spacer mutual codrugs are as follows:

Step I: Synthesis of chloroacetyl ester of phytoalcohol/phenols

A reaction mixture containing phytoalcohol/phenols (10 mmol), TEA (0.7 ml, 10 mmol) in dried chloroform (20 ml) was stirred in ice bath at −10°C. To this reaction mixture chloroacetyl chloride (0.8 ml, 10 mmol) in dry chloroform, 25 ml was added dropwise at −10°C, then stirred at room temperature for 8 hr. Then afterward workup was done with HCl (5%, 3 × 50 ml), NaOH (5%, 3 × 50 ml), and finally with brine solution (2 × 50 ml). The organic layer was dried over sodium sulfate. The product was purified by column chromatography by gradient elution with methanol in chloroform, using silica gel (80–120 mesh) to obtain the respective chloroacetyl derivatives of respective phytophenol/alcohol.

Step II: Synthesis of ketoprofen–phytoalcohol/phenols mutual codrugs with glycolic acid spacers (IIIa–h)

The respective chloroacetyl derivative of phytophenol/alcohol derivatives from above reaction was mixed with sodium iodide (0.749 g, 10 mmol), DMF (25 ml) as the solvent at 0°C followed by few drops of TEA. Then, ketoprofen (2.54 g, 10 mmol) in DMF (25 ml) was added dropwise at 0°C and then stirred at room temperature overnight. To this mixture ice-cold water was added and then extracted with ethyl acetyl (4 × 25 ml). The combined organic layers were worked up with HCl (5%, 3 × 50 ml), NaOH (5%, 3 × 50 ml), and finally with brine solution (2 × 50 ml) and dried over sodium sulfate. The product was purified by column chromatography by gradient elution of ethyl acetate in *n*-hexane up to 6% using silica gel (80–120 mesh) to obtain the respective ketoprofen–antioxidants ester codrugs with the glycolic spacer (**IIIa–h**) (Table 2).

The general chemical structures of the synthesized mutual codrugs of ketoprofen (**I**) with various phytophenols/alcohol through

the glycolic acid spacer (-OCH_2COO) are **IIIa–h** and their respective Ar/R are shown in Table 2.

4.1.5 | Chemical characterization of the synthesized codrugs–OCH_2COO–antioxidant codrugs

Ketoprofen–thymol with spacer (KTS), 2-(2-isopropyl-5-methylphenoxy)-2-oxoethyl-2-(3-benzoylphenyl)propanoate (IIIa)

IR (KBr, ν_{max}, cm^{-1}): 3460 (Ar- C-H st), 2985 (aliph.- C-H st), 1735 (C=O ester), 1649 (C=O ketone), 1457 (aromatic C=C), 1440 (C-C bend), 1231 and 1043 (C-O). ^{1}H-NMR ($CDCl_3$): 7.8–7.7 (3H, m, Ar-H), 7.6 (dt, 1H, Ar-H), 7.6–6.1 (2H, m, Ar-H), 7.5–7.4 (3H, m, Ar-H), 6.7–6.6 (3H, m, Ar-H), 2.3 (3H, s, Ar-CH_3), 2.95–2.90 (1H, m, $CH(CH_3)_2$ thymol), 3.86–3.79 (1H, q, $CHCH_3$), 4.90–4.73 (2H, s, O–CH_2-COO), 1.3 (6H, d, $CH(CH_3)_2$ thymol), 1.6 (3H, s, CH-CH_3). ^{13}C-NMR ($CDCl_3$): 20.6 (Ar-CH_3), 22.8 (CH-CH_3), 26.8 ($CH(CH_3)_2$ thymol), 60.7 (O-CH_2-COO), 121.79–136.49 (Ar-Cs), 167.0 (CH_2C=O), 176.14 (CH_3CHC=O), 196.97 (Ar-C=OAr). MS (ESI): *m/z* 444 (M^+). Anal. calcd. for $C_{28}H_{28}O_5$: C, 75.65; H, 6.35 Found: C, 75.78; H, 6.48.

Ketoprofen–guaiacol with spacer (KGS), 2-(2-methoxyphenoxy)-2-oxoethyl-2-(3-benzoylphenyl)propanoate (IIIb)

IR (KBr, ν_{max}, cm^{-1}): 3631.7 (Ar-C-H st), 2985 (aliph.-C-H st), 1736 (C=O esters), 1647 (C=O, ketone), 1486 (aromatic C=C), 1231 (C-O st, ester), 750–789 (substituted Ar rings). ^{1}H-NMR ($CDCl_3$): 7.7–7.2 (9H, m, Ar-H ketoprofen), 7.1 (2H, d, Ar-H guaiacol), 7.0–6.9 (2H, t, Ar-H guaiacol), 5.24 (2H, s, O-CH_2-COO-), 3.9–3.8 (1H, q, CH-CH_3), 3.8 (3H, s, O-CH_3). ^{13}C-NMR ($CDCl_3$): 10.5 (CH-CH_3), 45.3 (Ar-CH_2 and $CHCH_3$), 52.2 (Ar-OCH_3), 61.5 (O-CH_2-COO), 128.3–141.0 (aromatic-Cs), 150.9 (Ar-C-OCH_3 and CH_2C=O), 174.7 (HC-C=O (OCH_2)), 177.6 (–C=O(OAr)), 196.7 (Ar-CO-Ar). MS (ESI): *m/z* 418 (M^+). Anal. calcd. for $C_{25}H_{22}O_6$: C, 71.76; H, 5.30 Found: C, 71.58; H, 5.42.

Ketoprofen–menthol with spacer (KMS), 2-((2-isopropyl-5-methylcyclohexyl)oxy)-2-oxoethyl-2-(3-benzoylphenyl)propanoate (IIIc)

IR (KBr, ν_{max}, cm^{-1}): 3429 (Ar-C-H st), 2985 (aliph.- C-H), 1735 (C=O ester), 1649 (C=O ketone), 1457 (Ar C=C st), 1371 (C-H bend CH $(CH)_3$), 1235 and 1043 (C-O ester), 936–730 (Ar-C-H bend). ^{1}H-NMR ($CDCl_3$): 7.8–7.7 (3H, m, Ar-H), 7.6 (1H, dt, Ar-H), 7.6–7.5 (2H, m, Ar-H), 7.5–7.4 (3H, m, Ar-H), 5.1 (2H, s O-CH_2-COO), 3.90 (1H, m, O-CH menthol), 3.8–3.7 (1H, q, $CHCH_3$), 1.9–1.6 (3H, d, $CHCH_3$), 1.82–1.77 (1H, m, CH $(CH_3)_2$), 1.52–1.39 (2H, m, CH_2 menthol), 1.11–0.97 (2H, m, CH_2 menthol), 0.92–0.88 (6H, d, $CH(CH_3)_2$), 0.8–0.7 (3H, d, CH_3 menthol). ^{13}C-NMR ($CDCl_3$): 16.42 (CH-CH_3 menthol), 18.45 ($CHCH_3$ ketoprofen), 21.09–22.10 ($CH(CH_3)_2$ menthol), 23.12 (CH_2 menthol), 26.63 ($CH(CH_3)_2$ menthol), 34.7 (CH_2 menthol), 45.22 (CH-CH_3 ketoprofen), 47.04 (CH menthol), 71.78 (O-CH menthol), 128.56–141.74 (Ar-Cs), 167.2 (O-CH_2C=O), 173.8 (ArC=OAr). MS (ESI): *m/z* 451 ($M+H^+$). Anal. calcd. for $C_{28}H_{34}O_5$: C, 74.64; H, 7.61 Found: C, 74.52; H, 7.78.

Ketoprofen–vanillin with spacer (KVS), 2-(4-formyl-2-methoxyphenoxy)-2-oxoethyl-2-(3-benzoylphenyl)propanoate (IIId)

IR (KBr, ν_{max}, cm^{-1}): 3460 (Ar-C-H st), 2985 (aliph. C-H st), 1735 (C=O ester), 1696 (C=O aldehyde), 1649 (C=O ketone), 1497 (Ar C=C st), 1440 (C-C bend), 1234 and 1042 (C-O ester), 936 (ArC-H bend). ^{1}H-NMR ($CDCl_3$): 9.9 (1H, s, CHO), 7.8–7.7 (3H, m, Ar-H), 7.6 (1H, dt, Ar-H), 7.6–7.5 (2H, m, Ar-H), 7.5–7.4 (2H, m, Ar-H vanillin), 7.40 (3H, m, Ar-H), 7.3–7.2 (1H, m, Ar-H vanillin), 4.9–4.7 (2H, q, O-CH_2COO), 3.9 (3H, s, Ar-OCH_3 vanillin), 3.9–3.7 (1H, q, $CHCH_3$), 1.6 (3H, d, $CHCH_3$). ^{13}C-NMR ($CDCl_3$): 19.6 (CH-CH_3), 40.4 ($CHCH_3$), 55.2 (Ar-OCH_3), 61.0 (O-CH_2-COO), 122–136 (Ar-Cs), 141.2 (Ar-C-OCH_3), 150.5 (Ar-C-OC=O), 167.3 (CH_2C=O), 176.6 (CH_3CHC=O), 197.2 (ArC=OAr). MS (ESI): *m/z* 446 ($M+H^+$). Anal. calcd. for $C_{26}H_{22}O_7$: C, 69.95; H, 4.97 Found: C, 69.78; H, 4.85.

Ketoprofen–eugenol with spacer (KES), 2-(4-allyl-2-methoxyphenoxy)-2-oxoethyl-2-(3-benzoylphenyl)propanoate (IIIe)

IR (KBr, ν_{max}, cm^{-1}): 3018 (Ar-C-H), 2957 (aliph. C-H), 1737 (C=O esters), 1235 and 1044 (C-O), 1650 (C=O ketone), 1452 (Ar C=C). ^{1}H-NMR ($CDCl_3$) δ: 7.7–6.7 (12H, m, Ar-H ketoprofen and eugenol), 5.1 (2H, m, CH_2CH=CH_2), 6.7 (1H, m, CH_2CH=CH_2), 5 (2H, q, COO-CH_2-C=O), 3.9–3.8 (1H, q, CH-CH_3), 3.8 (3H, s, Ar-OCH_3), 3.3 (2H, d, Ar-CH_2CH=CH_2), 1.5 (3H, d, CH-CH_3). ^{13}C-NMR (ppm): 18.7 (CH-CH_3), 30 (CH-CH_3), 55.0 (Ar-OCH_3 and Ar-CH_2), 60.5 (O-CH_2-CO), 116.1 (CH=CH_2), 138.0 (CH_2CH=CH_2), 112.7–140.6 (Ar-Cs), 150.0 (Ar-C-OCH_3), 196.5 (Ar-C=O Ar). MS (ESI): *m/z* 458 (M^+). Anal. calcd. for $C_{28}H_{26}O_6$: C, 73.35; H, 5.72 Found: C, 73.18; H, 5.80.

Ketoprofen–sesamol with spacer (KSeS), 2-(benzo[*d*][1,3]-dioxol-5-yloxy)-2-oxoethyl-2-(3-benzoylphenyl)propanoate (IIIf)

IR (KBr, ν_{max}, cm^{-1}): 3081 (Ar-C-H), 2985 (aliph. C-H), 1739 (C=O ester), 1235 and 1044 (-OCH_3), 1232 and 1042 (C-O), 1647 (C=O ketone), 1486 (C=C), 937–730 (Ar-C-H). ^{1}H-NMR ($CDCl_3$): δ 7.5–7.8 (9H, m, Ar-H ketoprofen), 3.8 (1H, q, $CHCH_3$), 1.7–1.5 (3H, d, $CHCH_3$), 5.2 (2H, s, O-CH_2-COO), 6.6 (1H, d, Ar-H sesamol), 6.7 (1H, d, Ar-H sesamol), 6.8 (1H, ddAr-H), 5.9 (2H, s, CH_2 sesamol). ^{13}C-NMR (ppm): 16.3 ($CHCH_3$ ketoprofen), 40.2 (CH-CH_3 ketoprofen), 191.4 (ArC= OAr), 172.2 (HC-C= O(OAr)), 167.3 (O-CH_2C=O), 127–138 (Ar-Cs), 104–148 (Ar-C sesamol), 101.4 (OCH_2O sesamol. MS (ESI): *m/z* 432 (M^+). Anal. calcd. for $C_{25}H_{20}O_7$: C, 69.44; H, 4.66 Found: C, 69.30; H, 4.52.

Ketoprofen–curcumin with spacer (KCuS), 2-(4-((1*E*,6*E*)-7-(4-hydroxy-3-methoxyphenyl)]-3,5-dioxohepta-1,6-dien-1yl)-2-methoxyphenoxy)-2-oxoethyl-2-(3-benzoylphenyl)propanoate (IIIg)

IR (KBr, ν_{max}, cm^{-1}): 3081 (Ar-C-H), 2985 (aliph. C-H), 1739 (C=O ester), 1647 (C=O ketone), 1486 (C=C), 1235 and 1044 (C-O), 937–730 (Ar-C-H bend). ^{1}H-NMR ($CDCl_3$) (*J* in Hz): δ 7.8–7.4 (9H, m, Ar-H ketoprofen), 7.60 (2H, s, CH=CH-Ar), 7.30 (1H, s, Ar-H curcumin), 7.2–7.1 (2H, d, Ar–H), 6.9 (2s O=C-CH=CH-Ar), 6.8–6.9 (2H, d, Ar-H

curcumin), 5.4 (1H, s, phenolic-OH), 5.0 (2H, s, O-CH_2-COO), 4.6–4.5 (2H, s, O=C-CH_2C=O), 3.8 (1H, q, $CHCH_3$), 1.6 (3H, d, $CHCH_3$). ^{13}C-NMR ($CDCl_3$ in ppm): 14.1 ($CHCH_3$ ketoprofen), 40.2 (CH-CH_3 ketoprofen), 56.5 (Ar-O-CH_3), 62.3 (O-CH_2-C=O), 111–151 (Ar-C curcumin), 128–135 (Ar-C ketoprofen), 130.4 (ArCH=$CHCH_2$), 143.1 (Ar-CH=CH-CH_3), 167.3 (O-CH_2C=O), 174.4 (HC-C=O(OAr)), 180.9 (CH_2C=O), 199.2 (-C(=O)-C(=O)-). MS (ESI): *m/z* 462 (M^+). Anal. calcd. for $C_{39}H_{34}O_{10}$: C, 70.69; H, 5.17 Found: C, 70.50; H, 5.28.

Ketoprofen–gallic acid with spacer (KGaS), 4-(2-((2-(3-benzoylphenyl]propanoyl)oxy)acetoxy-3,5-dihyroxybenzoic acid (IIIh)

IR (KBr, ν_{max}, cm^{-1}): 2450–3245 (COOH), 3026 (Ar-C-H), 2931 and 2883 (aliph. C-H), 1235 and 1044 (-OCH_3), 1718 (C=O Ester), 1232 and 1042 (C-O ester), 1647 (C=O ketone), 1587 (C=C), 2848 (Ar-O-CH_3), 937–930 (Ar-C-H). ^{1}H-NMR ($CDCl_3$): δ 9.5 (1H –COOH gallic acid), 7.8–7.4 (9H, m, Ar-H ketoprofen), 7.3 (2H, s, Ar-H, gallicacid), 5.35 (2H, s, phenolic-OH), 5.0 (2H, s, O-CH_2-COO), 3.8 (6H, s, Ar-O-CH_3 Curcumin), 3.78 (1H, q, $CHCH_3$), 1.61 (3H, d, $CHCH_3$). ^{13}C-NMR (in ppm): 14.3 ($CHCH_3$ ketoprofen), 44.1 (CH-CH_3 ketoprofen), 127–132 (Ar-C ketoprofen), 62.4 (O-CH_2C=O), 178.2 (HC-C=O (OAr)), 136–138 (Ar-C gallic acid), 169.4 (-COOH). MS (ESI): *m/z* 464 ($M+H^+$). Anal. calcd. for $C_{25}H_{20}O_9$: C, 64.65; H, 4.34 Found: C, 64.52; H, 0.23.

4.2 | Physicochemical studies

4.2.1 | Solubility studies

An excess amount of each compound was added to 10 ml of phosphate buffer (pH 7.4) in a screw cap test tube and shaken for 24 hr at 37 ± 0.5°C in water bath shaker. Solutions were then filtered through Whatman filter paper after appropriate dilution in the same buffer and it was analyzed spectrophotometrically for the amount of codrug. The solubility studies data is reported in Table 1.

4.2.2 | Partition coefficient determination

The partition coefficients of the synthesized compounds were determined in octanol/phosphate buffer (pH 7.4) at 37 ± 0.5°C using the shake flask method. Octanol and phosphate buffer (pH 7.4) were mutually saturated by shaking overnight. The system was left undisturbed for half an hour and the layers were separated. A saturated solution of each codrug was prepared in *n*-octanol (5 ml). Then an equal volume of phosphate buffer (5 ml) was added to the solution in conical flasks. The sealed flasks were kept for shaking in a water bath shaker maintained at 37 ± 0.5°C or 24 hr. After shaking the two phases were separated by centrifugation at 3000 rpm for 10 min. Then both the phases were analyzed spectrophotometrically. Partition coefficient is calculated as:

$$\text{Partition coefficient } (P) = \frac{\text{Concentration of drug in octanol} \times \text{Dilution factor}}{\text{Concentration of drug in buffer}}$$

4.3 | Kinetics of hydrolysis study

4.3.1 | Chemical stability

The chemical stability (in vitro hydrolysis) study was carried out in non-enzymatic simulated gastric fluid (SGF) of pH 1.2 and in nonenzymatic simulated intestinal fluid (SIF) of pH 7.4 in isotonic buffers.[23] SGF is pH 1.2 HCl solution prepared by combining 0.2 M KCl solution with 0.2 M HCl solution, while SIF is pH 7.4 monobasic potassium phosphate buffer solution. The total buffer concentration was 20 mM and constant ionic strength of 0.5 M for each sample was maintained by adding KCl.

The hydrolysis of the codrug was initiated by dissolving 10 mg of the codrug in 90 ml of preheated SGF (pH 1.2), or in SIF (pH 7.4). The solutions were sealed in screw-capped glass vials and then placed into a thermostatically controlled water bath at 37 ± 0.5°C. Then 10 ml of the solution was withdrawn from each test tube at 15, 30, 60, 120, 240 and 480 min and transferred to microcentrifuge tubes, then centrifuged at 3000 rpm for 15 min. From this 5 ml of clear supernatant was taken and measured by UV-spectroscopy for the amount of parent NSAID (ketoprofen), released after the hydrolysis in buffer solutions at 260 nm. Pseudo-first order rate constants (K_{obs}) and half-lives ($t_{1/2}$) were determined by using the equations:

$$K_{obs} = \text{slope} \times 2.303,$$
$$t_{1/2} = 0.693/K_{obs}.$$

4.3.2 | Enzymatic hydrolysis study (80% human plasma)

The hydrolysis studies were carried out in 80% human plasma fractions with isotonic phosphate buffer (pH 7.4) at 37 + 0.5°C as per the reported procedure with some modification.[46,47] Human plasma fraction was obtained by centrifugation of the blood samples containing 0.3% citric acid at 3000 rpm for 20 min. Human plasma fractions (4 ml) were diluted with 1 ml of phosphate buffer (pH 7.4, isotonic) to give the final volume of 5 ml of diluted human plasma 80%.

The reactions were started by adding 0.5 ml of stock solution (1000 μg/ml) of the codrugs in ethanol to 5 ml of preheated, diluted human plasma (80%). Then the samples were withdrawn at appropriate time intervals (15, 30, 60, 120, 240 min), further diluted with phosphate buffer and then analyzed spectrophotometrically at 260 nm for the appearance of the free drug (ketoprofen) with time. The rate of hydrolysis (K_{obs}) and $t_{1/2}$ were calculated using the equations:

$$K_{obs} = \text{slope} \times 2.303,$$
$$t_{1/2} = 0.693/K_{obs}.$$

4.4 | Pharmacological studies

4.4.1 | Anti-inflammatory activity

The parent drug ketoprofen in the dose of 20 mg/kg of body weight was used as a reference standard. The doses of the codrugs were chosen on equimolar bases as shown in Table 5. Carrageenan-induced hind paw edema method was used to test for anti-inflammatory activity.[50] The edema is expressed as percentage increase in left hind paw in comparison to the un-injected right hind paw. Albino rats, weighing 200–250 g of either sex, were selected and divided into groups of six each. Paw edema was induced in rats by means of subplantar injection into the left hind paw of rats by injecting 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 (as the control). Ketoprofen and other test drugs were administered orally 1 hr before the irritant. The paw volume up to a fixed mark at the level of lateral malleolus was measured using plethysmometer after 2 hr, 4 hr of the carrageenan injection. Increase in paw volume was calculated as:

$$\% \text{ increase in paw volume} = V_L - V_R / V_R \times 100,$$

where V_L = Volume of left paw

V_R = Volume of right paw (control)

The mean + SEM values were calculated for each group for the % edema.

4.4.2 | Analgesic activity

Writhing tests in mice are the most common method for measuring peripheral analgesic activity which is determined using acetic acid-induced writhing assay procedure.[51,52] To induce writhing freshly prepared acetic acid solution (1% w/v in saline pH = 2.7, 10 ml/kg) was given by intraperitoneal (ip) injection. Different treatment groups of rats were made as shown in Table 5 containing six animals in each group. Ketoprofen (20 mg/kg) and the test codrugs were administered in the equimolar doses. All these were administered by the oral route, emulsified in 0.5% sodium carboxymethyl cellulose vehicle, 30 min before the introduction of acetic acid. The writhing responses (constriction of the abdomen, turning of trunk, and extension of hind limbs) were recorded starting from 3 min after injection of acetic acid till 20 min. The degree of analgesia was expressed as % inhibition as compared to the average of the vehicle-treated control group.

$$\% \text{ inhibition} = 1 - (N_t / N_c) \times 100,$$

where, N_c = Average number of writhes incontrol,

N_t = Average number of writhes in drug treated rats.

The control group (vehicle treated group) showed an average writhing of 78 + 1.52.

4.4.3 | Antiulcer/gastrointestinal erosion assay (GIER)

Different treatment groups of albino rats of 6 animals each (150–250 g) were made. The ulcer-inducing dose (four times of their anti-inflammatory dose) of ketoprofen (80 mg/kg) and the equimolar doses of the test compounds as shown in Table 7 was introduced by oral route once daily for four days as a suspension in 0.5% CMC in aqueous vehicle used in a volume of 0.5 ml/100 g of animal weight. After the administration of the fourth dose, the food was removed and using chloroform/ether fumes the animals were killed. At necropsy, the stomachs were removed and opened along the greater curvature and were examined under the magnifying lens for lesions.[53] The results are as shown in Table 7 and the grades for observed lesions are given in Table 6.

4.4.4 | Antioxidant studies (in vitro)

To assess the free radical scavenging activity of ketoprofen–OCH_2COO–phytophenols/codrugs, 1,1-diphenyl-2-picrylhydrazyl radical (DPPH) assay was carried out.[54] DPPH is a stable free radical having a purple color that after reduction, for example with some antioxidants, gets reduced and changes its color to yellow. IC_{50}-values are used to quantify the antioxidant activity. IC_{50} value, calculated from the inhibition curve, is the concentration of the sample (in μg/ml) required to scavenge 50% DPPH free radical. A 100 μM solution of DPPH in methanol was added to the separate solutions of thymol, guaiacol (10–100 μg/ml), eugenol (10–100 μg/ml), vanillin (10–100 μ/ml), sesamol (10–100 μg/ml), gallic acid (10–100 μg/ml), curcumin (10-100 μg/ml), and the phytoalcohol menthol (10–100 μg/ml). The absorbance was read at 515 mm after 20 min. The radical scavenging activity was expressed as:

$$\% \text{ DPPH radical scavenging} = \frac{\text{Ac–As} \times 100}{\text{Ac}},$$

where Ac = absorbance of control (*i.e.* of DPPH without sample),

As = absorbance of sample solution.

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CONFLICT OF INTERESTS

The authors declare that they have no conflict of interests.

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