Prodrug Designing of NSAIDs

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Abstract: Non-steroidal anti-inflammatory drugs (NSAIDs), commonly used for the treatment of chronic inflammatory diseases suffer from several undesired side effects, the most important being gastrointestinal (GI) irritation and ulceration. The prodrug designing is one of the several strategies used to overcome this drawback. The rationale behind the prodrug concept is to achieve temporary blockade of the free carboxylic group present in the NSAIDs till their systemic absorption. In this paper, a review on the concept of prodrugs designing of NSAIDs to improve their efficacy and reduce the toxicity is being presented.

Key Words: NSAIDs, NO release, amides, esters, inflammation, prodrugs, prostaglandins, ulceration.

INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used for the treatment of chronic inflammatory diseases, such as arthritis. Prolonged administration of these drugs exhibit several undesired side effects; the most important are gastro-intestinal irritation and ulceration which represent still an unsolved therapeutic problem. The development of a gastrointestinal tract (GIT)-safe anti-inflammatory therapy for the treatment of disease of joints presents a unique challenge. It has been more than a hundred years since Felix Hoffman, working at Bayer Industries, reported the successful synthesis of acetylsalicylic acid as the first non-steroidal anti-inflammatory drug (NSAID) [1, 2]. Approximately 40 years after the introduction of aspirin Doutwaite and Lintott provided endoscopic evidence that aspirin could cause gastrointestinal (GI) mucosal damage [3]. Introduction of more potent agents with an even greater propensity for toxic side effects increased the awareness about NSAID-induced gastro-duodenal ulceration and provided impetus for development of effective NSAIDs with more favorable GI safety profile.

PATHOGENESIS OF NSAID-INDUCED GASTRO-DUODENAL MUCOSAL INJURY

Clinical use of most of the available acidic NSAIDs is strongly limited by their GI side effects which range in both severity and frequency from relatively mild to more serious and potentially life threatening states, such as GI ulceration and hemorrhage [4]. It is a well accepted fact that the GI side effect of acidic NSAIDs is a result of two different mechanisms [5-8].

a) Local Effect on GI Tract

The first mechanism involves a local action comprising of a direct contact effect and an indirect effect on the GI mucosa [5-8]. The direct effect can be attributed to the local inhibition of prostaglandin (PG) 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 H^+ ions from the lumen into the mucosa. Topical irritation by the free carboxylic group of the NSAIDs is considered an important factor in establishing superficial stomach erosion, particularly in the corpus region of the stomach.

b) Systemic Effects

The second mechanism is based on the generalized systemic action occurring after absorption and can be manifested even after intravenous dosing [8, 9]. The systemic effects are manifested due to inhibition of synthesis of gastric PGs like PGI_2 and PGE_2.

PRODRUGS OF NSAIDs

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. Prodrugs are pharmacologically inactive derivatives of active agents, which undergo chemical and/or enzymatic biotransformation resulting in the release of active drug after administration. The metabolic product (i.e. parent drug) subsequently elicits the desired pharmacological response [10, 11].

Most prodrugs of NSAIDs have been prepared by derivatization of the carboxyl group. The esters have dominated prodrug research because they have the ideal characteristic of exhibiting reasonable *in vitro* chemical stability which allows them to be formulated with adequate shelf lives. In addition, by virtue of their ability to function as esterase substrates, esters are suitably labile, *in vivo* [12, 13].

With this aim different promoeities have been taken into consideration to design new efficacious NSAID prodrugs. In the following sections, various ester and amide derivatives of NSAIDs will be discussed.

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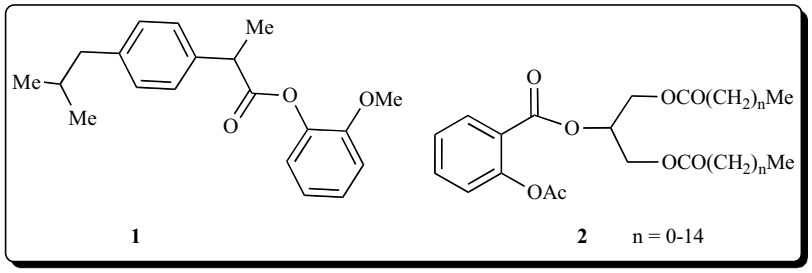
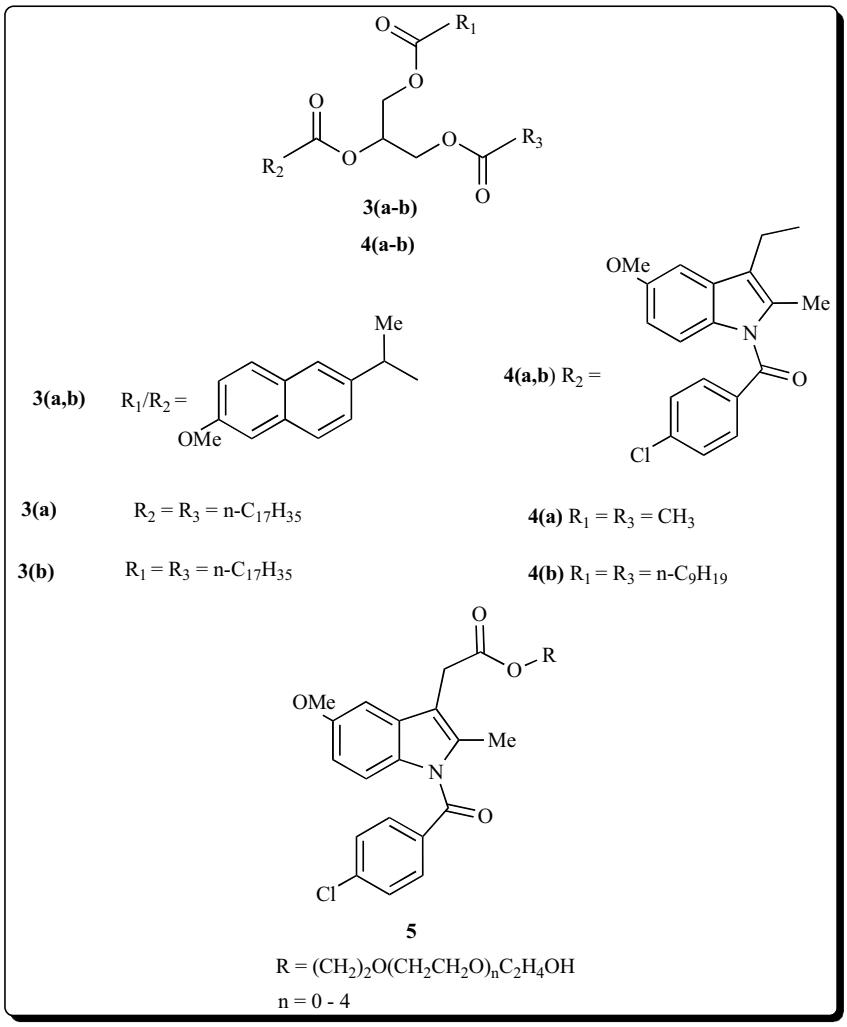


Cioli *et al.* [14] have investigated the toxicological and pharmacological profile of ibuprofen guiacol ester **1**. The gastrointestinal toxicity, behavioural disorders and acute toxicity of the ester were much reduced in comparison to ibuprofen. The ester and the parent drug at equimolar doses, were equally effective in edema and fever. The ester was found to be better tolerated than its parent drug because of its peculiar pharmacokinetics i.e. the slow release of the parent drug, which reduced its local and general toxicity.

Paris *et al.* [15] prepared a series of 1,3-bisalkanoyl-2-(O-acetylsalicyloyl)glycerides, (triglycerides of aspirin) **2** having aspirin at 2 position of glycerol and fatty acids at 1 and 3 positions. The studies for presence of lesions in stomach showed that the derivatives in which fatty acids are of intermediate chain length (C_4-C_{12}) did not cause gastric lesions and had essentially all the systemic activity associated with aspirin.

Triglyceride derivatives [16, 17] of naproxen **3 (a-b)** and indomethacin **4 (a-b)** have been prepared. Comparison of the 2-glyceride of naproxen **3b** with naproxen for gastric irritation, as determined by the minimum chronic dose producing occult blood in either faeces or urine in dog, gave a dose ratio of 3 in favor of the 2-glyceride **3b**. The 2-glyceride **4b** of indomethacin showed a 2.5 to 3.0 fold improvement in the therapeutic index.

The methyl esters of salicylic acid, diflunisal, flufenamic acid, indomethacin, diclofenac and tolmetin were synthe-



sized [18] and found to be effective in reducing interaction of the irritant NSAIDs in the acidic milleu of the stomach with drug sensitive mucosal and parietal cells.

Indomethacin farnesil, a prodrug of indomethacin has been reported to cause less gastric damage than indomethacin and loxoprofen due to its less potency for inhibiting the gastric mucosal prostaglandins [19].

With the aim of designing potential NSAID prodrugs Caprariis *et al.* [20] considered oligoethylene glycols as attractive promoiteies because, (i) they are known to have good biocompatibility [21], (ii) they could give prodrugs with enhanced aqueous as well as lipid solubility compared to the parent drug so as to increase GI absorption [22], and (iii) they cause enhanced residency period of NSAIDs into the system since they prevent enzymes from attacking the drug [23]. Five different oligoethylene ester derivatives **5** of indomethacin were synthesized and evaluated. All the esters were found to be significantly less irritating to gastric mucosa than indomethacin after oral administration with better or similar anti-inflammatory and analgesic activity [20].

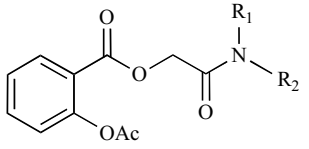
Ethyl esters of flurbiprofen *L*-arginine, flurbiprofen *L*-lysine and flurbifen p-guanidino-L-phenylalanine were synthesized and evaluated [24] for their availability as prodrugs for flurbiprofen. They were found to release the parent drug *in vitro* upon enzymatic hydrolysis.

Succinamide esters and glycineamides of naproxen, ibuprofen, ketoprofen, aspirin, diclofenac and indomethacin have been synthesized by Singh *et al.* [25]. The succinamide esters retained their anti-inflammatory property whereas the glycineamides exhibited lower activity as compared to those of the parent drugs. The glycineamides showed no hydrolysis at lower pH and in gastric fluid till 2 hours and had less GI toxicity than succinamide esters which exhibited complete hydrolysis within 15 minutes in the gastric fluid.

A series of glycolamides **6 (a-l)**, glycolate, (acyloxy)methyl, alkyl and aryl esters **7 (a-j)**, of acetylsalicylic acid were synthesized and evaluated [26] as potential prodrugs of aspirin. The N,N-disubstituted glycolamide esters were found to be rapidly hydrolysed in human plasma resulting in the formation of aspirin as well as the corresponding salicylate esters which in turn hydrolyzed rapidly to salicylic acid.

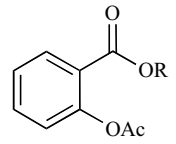
The kinetics of hydrolysis of glycolamide esters **8 (a-c)** of indomethacin was studied [27] to assess the possibility of designing a water-soluble and solution-stable prodrug of indomethacin suitable for parenteral or ocular administration. The prodrugs degraded both, at its ester group linkage and at the indole amide linkage of indomethacin, showing a pronounced water catalysed hydrolysis leading to the conclusion that design of an indomethacin ester prodrug with a stability allowing formulation of a ready-to-use aqueous solution may be difficult.

A series of novel ω-(N,N,N,-trialkylammonium)alkyl ester and thioester derivatives of eleven non-steroidal anti-



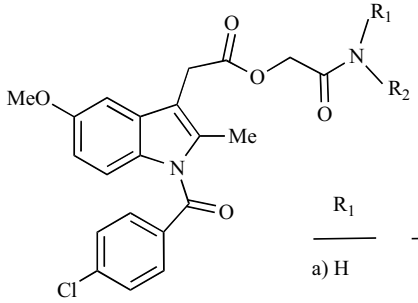
6 (a-l)

	R_1	R_2
a)	H	H
b)	H	C_2H_5
c)	H	CH_2CONH_2
d)	H	$CH_2COOC_2H_5$
e)	CH_3	CH_3
f)	C_2H_5	C_2H_5
g)	C_3H_7	C_3H_7
h)	i-C_3H_7	i-C_3H_7
i)	C_6H_{11}	C_6H_{11}
j)	CH_3	C_2H_4OH
k)	CH_3	CH_2CONH_2
l)	CH_3	$CH_2COOC_2H_5$



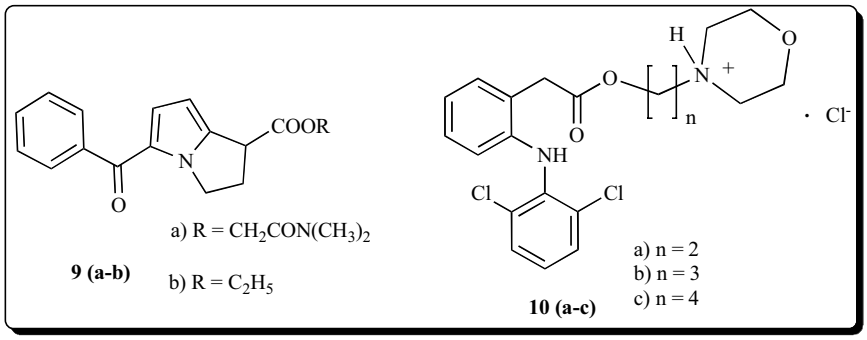
7 (a-j)

	R
a)	CH_3
b)	C_6H_5
c)	C_6H_4- 2-COOH
d)	C_6H_4- 4-$NHCOCH_3$
e)	CH_2SCH_3
f)	$CH_2SO_2CH_3$
g)	$CH_2SO_2CH_3$
h)	$CH_2COOC_3H_7$
i)	CH_2COOCH_3
j)	$CH_2COOC_2H_5$



8 (a-c)

	R_1	R_2
a)	H	H
b)	CH_3	CH_3
c)	CH_3	C_2H_5OH



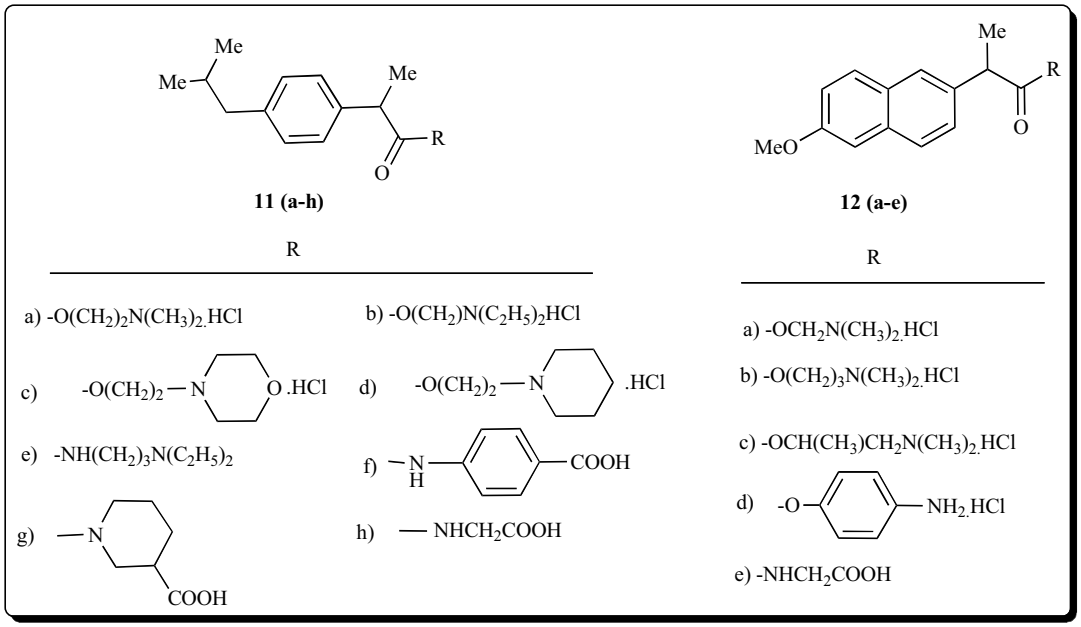
inflammatory carboxylic acid agents (naproxen, ketorolac, indomethacin, ibuprofen, sulindac, ketoprofen, flufenamic acid, mefenamic acid, zomepirac, etodolac and tifurac) were prepared and evaluated for their anti-inflammatory, analgesic and gastrointestinal erosive properties [28]. The pharmacokinetics of ibuprofen ethylcarbonate and naproxen ethylcarbonate, two new prodrugs of ibuprofen and naproxen in dogs, was reported by Samara *et al.* [29].

The *in vitro* skin permeabilities of ketorolac and its two ester analogs **9 (a-b)** as prodrugs through human cadaver skin were investigated [30]. The [N,N-(dimethylamino)carbonyl]methyl ester **9a** appeared to be a better ester prodrug than the simple ethyl ester **9b** prodrug as it exhibited relatively higher skin flux and faster enzymatic hydrolysis in human serum to liberate the parent drug.

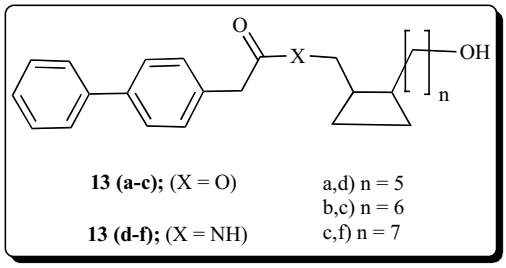
Morpholinoalkyl esters of naproxen and indomethacin were synthesized and evaluated *in vitro* and *in vivo* for their potential use as prodrugs for oral delivery [31]. The prodrugs were found to be 30-36 % more bioavailable orally than the parent drugs. A series of morpholinoalkyl ester prodrugs **10 (a-c)** of diclofenac were synthesized by Tamara *et al.* [32] and evaluated *in vitro* and *in vivo* for their potential use as prodrugs for oral delivery. All these esters were reported to exhibit a rapid bioconversion in rat plasma and were significantly less irritating to the gastric mucosa than the parent drug.

Many ester **11 (a-d)**, **12 (a-d)** and amide **11 (e-h)**, **12e** prodrugs of ibuprofen and naproxen were synthesized and biologically evaluated by Shanbhag *et al.* [33]. The ulcerogenicity of the prodrugs **11a**, **12a**, **11h**, and **12d** was less than the respective parent drugs. All the prodrugs were found to be less active than the parent NSAIDs in their anti-inflammatory efficacy.

Cyclodextrins (CyDs) are known to form inclusion complexes with various drug molecules wherein the complexes exist in equilibrium with the guest and host molecules in aqueous solution [34]. However, such a situation is disadvantageous when drug targeting is to be attempted because the complex would dissociate before it reaches the target organ. This problem could be overcome by covalent binding of the drug to CyDs. CyDs are known to be capable of hardly being hydrolyzed and absorbed during passage through the stomach and small intestine. However, they are fermented into small saccharides by colonic microflora and thus get absorbed in the large intestine [35]. This biodegradation property of CyDs has been exploited for site specific delivery of drugs to colon. Six 4-biphenylylacetic acid prodrugs, coupled to alpha, beta and gamma-cyclodextrins through an



ester or amide linkage, 6-O-[(4-biphenylyl)acetyl]-α/β/γ-cyclodextrins **13 (a-c)** and 6-deoxy-6-[(4-biphenylyl)acetyl]-α/β/γ-cyclodextrins **13 (d-f)** were prepared and investigated by Minami *et al.* [36] for their *in vivo* drug release behaviour in rat gastrointestinal tracts after oral administration. The results suggested that this approach can provide a versatile means for constructions of not only colon-specific delivery systems but also delayed-release system for certain drugs. A study on biphenylacetic acid bound to β-cyclodextrin through an ester **13b** or amide linkage **13e** suggested the potential of the ester prodrug **13b** for colon targeting [37].



Abordo *et al.* [38] carried the synthesis of 2-formylphenyl esters of indomethacin **14a**, ketoprofen **15**, ibuprofen **16** and aspirin **17a**, together with two 6-substituted-2-formyl **17b**, **17c** and two 2-acylphenyl aspirins **17d**, **17e** and 4-formylphenyl indomethacin **14b**. The 2-formylphenyl esters **14a**, **15**, **16**, **17a** were found to be more potent as anti-inflammatory agents than the parent compounds in the carrageenan-induced paw edema test. The n-butyl and n-octyl ester prodrugs of indomethacin did not show GIT and hepatic injury even after repeated oral administration in contrast to the severe irritating effect of the parent drug [39].

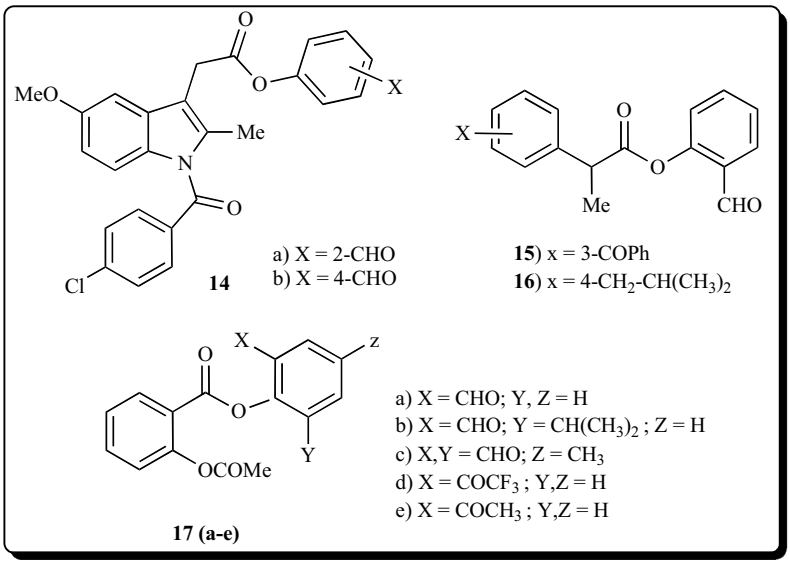
Jung *et al.* [40] reported a simple synthetic route for the preparation of amino acid conjugate of 5-aminosalicylic acid (5-ASA). *In vitro* and *in vivo* properties of 5-aminosalicylglycine (5-ASA-Gly) as a colon specific prodrug of 5-ASA were investigated using in rats as the test animals. Incubation of 5-ASA-Gly at 37°C with cecal and colonic contents released 65 % and 27 % of 5-ASA in 8 h, respectively. Free 5-ASA was not detected upon incubation of the conjugate with the homogenates of stomach or small intestine.

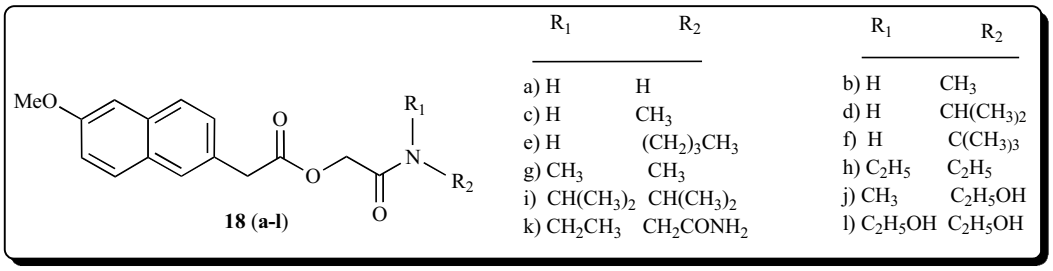
Various glycolamide ester prodrugs **18 (a-l)** of 6-MNA were synthesized and evaluated for the physicochemical properties, chemical stability and enzymatic hydrolysis in 80 % human plasma [41]. The chemically more stable disubstituted glycolamide esters **18 (g-l)** were more prone to enzymatic cleavage than the monosubstituted ones with half – lives ranging from 7s to 83s.

Bonina *et al.* evaluated two esters **19 (a-b)**, 1-ethyl-azacycloalkan-2-ones of indomethacin for their potential use as prodrugs for oral delivery [42]. Evaluation indicated that the esters represented potentially useful indomethacin prodrugs for oral administration since they were found to be stable in aqueous solution as well as in simulated gastric fluid with a fast enzymatic hydrolysis in rat plasma. The anti-inflammatory and analgesic activities of the parent drug were retained and the gastrointestinal irritation was notably inhibited by both the esters.

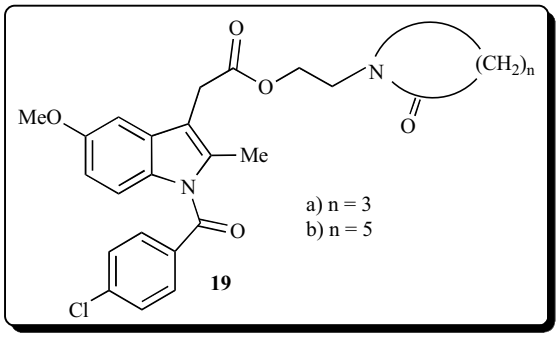
Mahfouz *et al.* synthesized ester prodrugs of aspirin, ibuprofen, naproxen and indomethacin using N-hydroxymethyl-succinimide and N-hydroxymethylisatin as promoeities to reduce their GI toxicity and improve bioavailability [43]. *In vivo* ulcerogenicity studies revealed that the synthesized ester prodrugs were significantly less irritating to gastric mucosa than the parent drugs.

Rautio *et al.* synthesized and evaluated various aminoacyloxyalkyl esters of naproxen and naproxenoxyalkyl diesters of glutamic acid and aspartic acid as potential prodrugs of naproxen for trans dermal delivery [44]. These prodrugs were shown to have higher aqueous solubilities and similar lipid solubilities in terms of octanol-buffer partition coefficients (log P) at pH 5.0, when compared with naproxen. Various aminoacyloxyalkyl esters [44], acyloxyalkylesters [45, 46] and diacylglyceryl ester [47] prodrugs of ketoprofen and naproxen have been reported with potential for improving dermal delivery of the parent drugs.





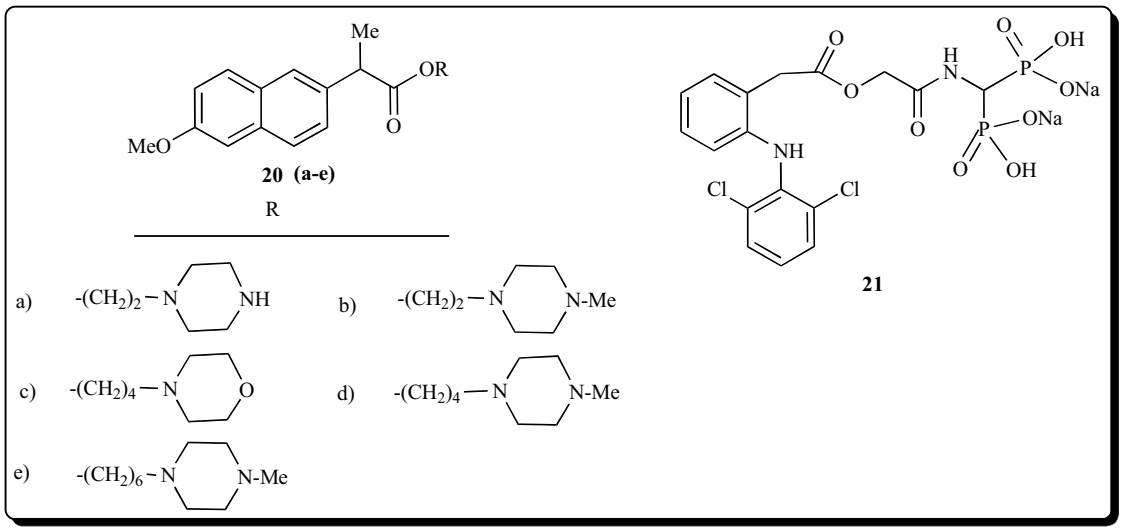
Morpholinyl and piperazinylalkyl esters **20 (a-e)** of naproxen have been reported as bioreversible topically administered dermal prodrugs of naproxen [48]. A 4 to 9 fold enhancement of permeation was observed for **20d** and **20b** when compared to naproxen at pH 7.4 and a 4 fold better permeation was observed for **20b** at pH 5.0. A novel 3-(N,N-diethylamino)propyl ester prodrug of indomethacin was found to be a potent anti-inflammatory agent with lower ulcerogenicity in stomach [49].

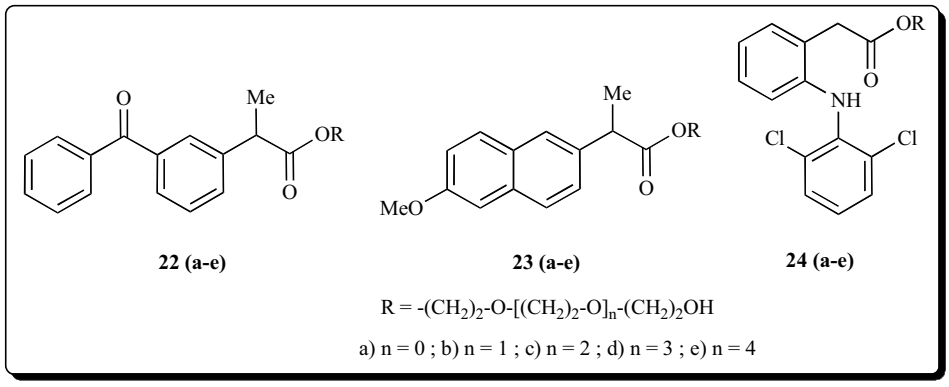


Biphosphonates, a class of compounds structurally related to pyrophosphate, are clinically used to treat various bone disorders, including osteoporosis. Biphosphonates are known to have high affinity for hydroxyapatite (a major component of osseous tissue) and osseous tissues accumulate biphosphonates in high concentrations. Based on the concept of Osteotropic Drug Delivery System, disodium 2-(2,6-dichloroanilino)phenylacetoxyacetamino- methylene biphosphonate **21** a biphosphonic prodrug of diclofenac was synthesized and investigated for its potency and controlled delivery of diclofenac to the bones in rats [50]. No side effect of gastrointestinal damage, typical of NSAIDs was observed, for this prodrug **21**. The bone specific delivery and sustained release properties of the prodrug could enhance the pharmacological effect of diclofenac for bone diseases, while simultaneously preventing adverse GI effects and increasing the patient compliance by decrease in frequency of its administration.

A new polymerizable drug derivative of diclofenac sodium was synthesized and characterized by Chandrasekar *et al.* [51]. The *in vitro* study showed that the drug release takes place predominantly at higher pH and in a sustained manner, as hypothesized, with complete drug absorption from the polymeric prodrug and a statistically significant decrease in ulcer scores was observed demonstrating its potential for site-specific and sustained delivery of diclofenac.

Polyoxyethylene esters of ketoprofen **22 (a-e)**, naproxen **23 (a-e)** and diclofenac **24 (a-e)** showed good stability in phosphate buffer (pH 7.4) and simulated gastric fluid (pH 2.0), and were readily hydrolyzed by human plasma. Anti-inflammatory activity of the esters was found to be similar to the parent drugs although at higher doses, and good analgesic activity was exhibited with significantly reduced gastric irritation even at higher doses [52]. These esters were also evaluated as dermal prodrugs [53]. An appreciable and sustained *in vivo* topical anti-inflammatory activity was observed for the ester prodrugs in the erythema model in human volunteers.

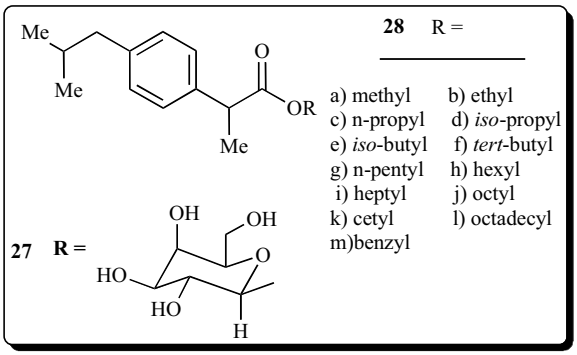




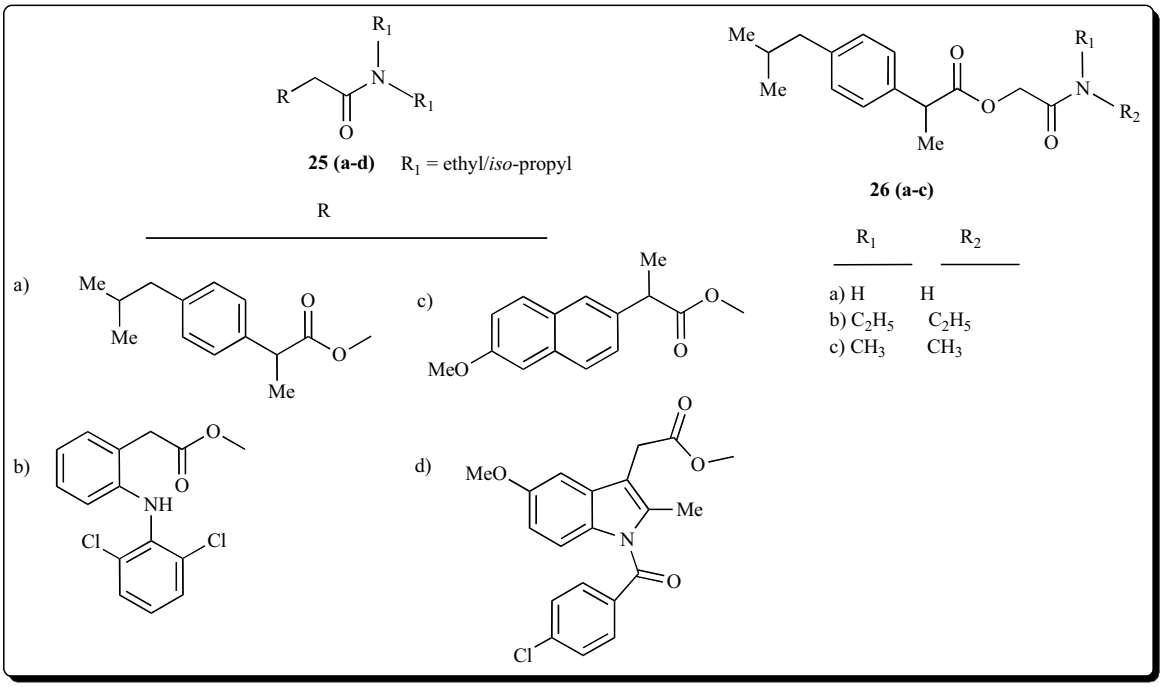
Khan *et al.* have evaluated the glycolamide ester prodrugs of ibuprofen **25a**, diclofenac **25b**, naproxen **25c** and indomethacin **25d** for their GI toxicity in rats [54]. Glycolamide esters **26 (a-c)** of ibuprofen were also synthesized and studied for different physicochemical, pharmacological and toxicological properties [55]. Hydrazide derivatives of naproxen, diclofenac, ibuprofen and indomethacin were synthesized and evaluated biologically in rodent model [56].

Ibuprofen β-D-glucopyranoside (**27**) has been reported by Khan *et al.* to possess superior anti-inflammatory and analgesic activities over the parent drug with significantly less ulcerogenicity [57]. Alkyl ester prodrugs of ibuprofen **28 (a-l)** have been reported by Bansal *et al.* [58] with significant improvement in the oral delivery of ibuprofen in terms of reduced gastroulcerogenicity and maintenance of pharmacological activity. These esters were also evaluated for their physicochemical properties and anti-inflammatory activity in carrageenan induced rat paw edema by topical route [59]. The benzyl ester prodrug **28m** showed a significantly reduced gastric ulcerogenicity at equimolar doses with retention of anti-inflammatory and analgesic activities [60].

Wang *et al.* [61] have co-polymerized ibuprofen, ketoprofen and naproxen with 2-hydroxyethylmethacrylate



(HEMA) with high methacrylate contents. The polymeric prodrug of ibuprofen retained the anti-inflammatory potency of ibuprofen whereas the prodrugs of ketoprofen and naproxen displayed greater potency to inhibit acute inflammatory processes than the free drug.



With the aim of extending drug action and shielding the carboxylic acid group Shaaya *et al.* have reported the synthesis and *in vivo* pharmacological evaluation of mixed anhydrides of ibuprofen with fatty acids of different chain length. The extended analgesic effect for over 24 hours in rodent model was found to be a function of fatty acid chain length [62].

Omar *et al.* have reported some N-hydroxymethylphthalimide esters of ibuprofen, naproxen and aspirin to be useful non-ulcerogenic prodrugs of acidic NSAIDs [63]. Two additional analogous cyclic amides, N-hydroxymethylsuccinimides **29-32** and N-hydroxymethylisatins **33-36** were synthesized as alternate promoieties to N-hydroxymethylphthalimide. In contrast to the derivatives, the parent drugs-treated groups were found to be ulcerogenic in stomach [64].

Ten prodrugs of ketorolac were synthesized by amidation with ethyl esters of aminoacids glycine, *L*-phenylalanine, *L*-tryptophan, *L*-valine, *L*-isoleucine, *L*-alanine, *L*-leucine, *L*-glutamic acid, *L*-aspartic acid and β-alanine. Marked reduction in ulcer index and comparable analgesic, anti-inflammatory activities were obtained in all cases as compared to ketorolac [65].

Ester prodrugs of ibuprofen synthesized using α-methyl, ethyl and propyl glucopyranosides as promoieties have been reported to undergo rapid cleavage inside the biological system and elicit a pharmacological profile quite similar to that of ibuprofen on oral administration, but, unlike the parent drug, they displayed reduced gastric ulceration [66]. For reducing the gastrointestinal toxicity associated with ibuprofen, ester prodrugs with 1,2,3-trihydroxypropane-1,3-dipalmitate/stearate were prepared and evaluated [67].

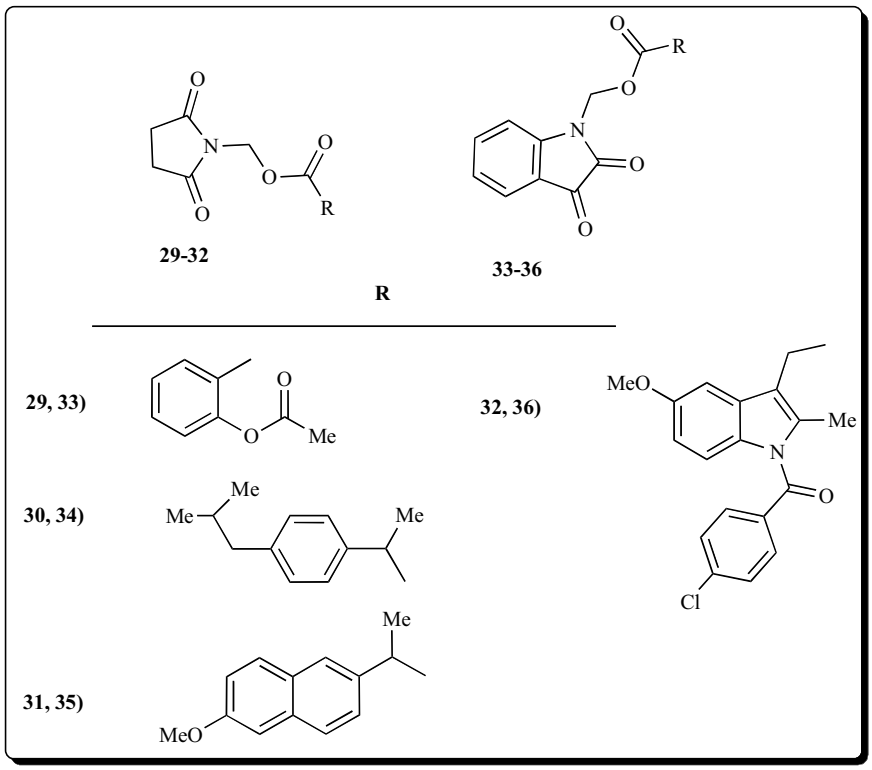
Ibuprofen, naproxen and ketoprofen were linked to chondroitin sulfate (ChS) *via* a PEG 1000 as spacer. The ketoprofen-ChS conjugate was found to be susceptible to degradation in presence of esterases and chondroitinase with the liberation of ketoprofen and Chs [68].

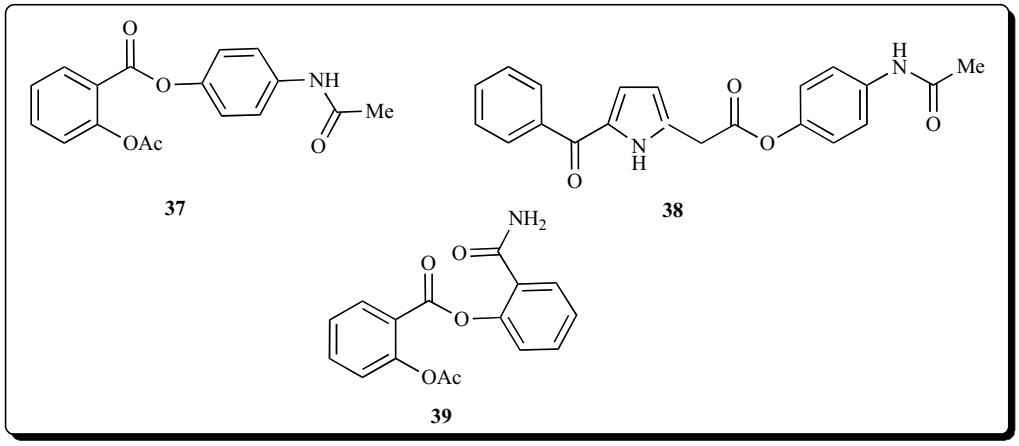
MUTUAL PRODRUGS

A mutual prodrug consists of two pharmacologically active agents coupled together covalently so that each acts as a promoiety for the other agent and *vice versa* [69,70]. The selected carrier may have the same biological action as that of the parent drug and thus might give synergistic action, or the carrier may have some additional biological action that is lacking in the parent drug, thus ensuring some additional benefit. The carrier may also be a drug that might help to target the parent drug to a specific site or organ or cells or may improve site specificity of a drug. The carrier drug may be useful to overcome some side effects of the parent drug as well.

Decreased gastrointestinal irritation with synergistic analgesic action was claimed by Croft *et al.* for benorylate **37** a mutual prodrug of aspirin and paracetamol, linked through ester linkage [71]. Mutual prodrugs [72, 73] of tolmetin with paracetamol **38**, and of aspirin with salicylamide **39** have been evaluated with the aim of abolishing the gastrointestinal toxicity of these drugs.

The drug conjugate **40** of flurbiprofen with a histamine H_2 receptor antagonists, N-[3-(3-(1-piperidinomethyl)phenoxy)propyl]-2-(2-hydroxyethylthio)acetamide was synthesized and investigated by Imai *et al.* for obtaining reduction in gastric damage [74]. A significant reduction in gastric toxicity in comparison to an equivalent dose of flurbiprofen





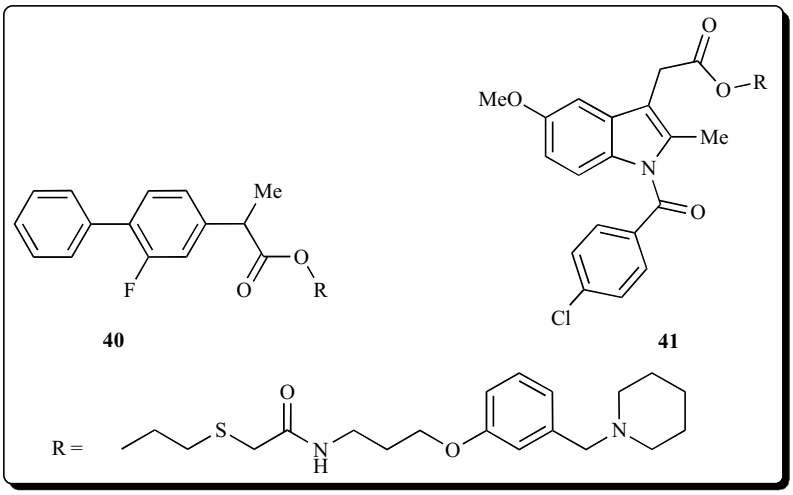
and methyl ester of flurbiprofen was observed with rapid plasma catalysed hydrolysis suggesting that the drug complex of flurbiprofen with H_2 antagonist is superior to simple ester or plain drug in its therapeutic profile. The ester prodrug 2-[N-[3-(3-(1-piperidinomethyl)phenoxy)propyl]carbamoylmethylthio]ethyl 1-(p-chlorobenzoyl)-5-methoxy-2-methylindol-3-acetate **41** of an H_2-antagonist and indomethacin was shown to be essentially similar to indomethacin in its anti-inflammatory potency that almost completely inhibited carrageenan-induced hind-paw edema with so low an ulcerogenicity that resulted in twenty-fold improvement in the ratio of anti-edema activity to ulcerogenicity [75].

During inflammation, reactive oxygen species (free radicals) are produced in an uncontrolled way causing tissue damage [76]. Melatonin, an antioxidant was reported to show protective effects in indomethacin induced gastric injury by virtue of its radical scavenging activity [77]. Based on this observation, Kourounakis *et al.* found it interesting to synthesize and evaluate amide derivatives of diclofenac, ibuprofen and indomethacin with a well known antioxidant cysteamine, exhibiting good anti-inflammatory and antioxidant activites and showing a significant reduction in ulcerogenicity [78].

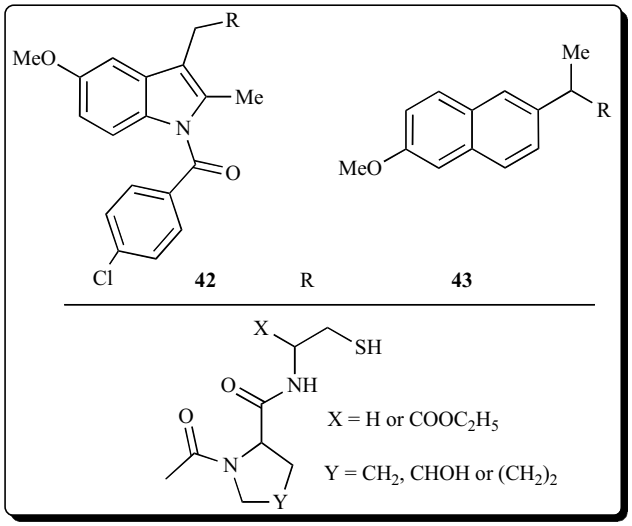
Glycine methyl ester conjugate of ketoprofen [79], and various conjugates of flurbiprofen [80] with amino acids like *L*-tryptophan, *L*-histidine, *L*-phenylalanine and *L*-alanine as mutual prodrugs were reported to have less ulcerogenicity with better antiinflammatory/analgesic action than their parent drugs. Mutual prodrugs of ibuprofen with paracetamol and salicylamide have been reported with better lipophilicity and reduced gastric irritancy than the parent drugs [81].

Naproxen, probenecid, diclofenac, ibuprofen and indomethacin were converted to hydrazide derivatives which were further condensed with β-keto esters to give pyrazolone derivatives. The hydrazide derivatives of probenecid and diclofenac were also reacted with biphenylacetic acid, an active metabolite of the anti-inflammatory drug fenbufen. The compounds were found to exhibit similar anti-inflammatory and analgesic potency when evaluated in rodent models [82].

With the aim of improving the therapeutic index through prevention of gastrointestinal irritation and bleeding, naproxen–propyphenazone esters were synthesized as mutual prodrugs [83]. Fadl *et al.* have reported the mutual prodrug of paracetamol and some acidic NSAIDs with faster rates of release of the corresponding NSAIDs ($t_{1/2}$ = 15-385 min) and paracetamol (1-140 min) [84]. A significant improvement in latency of pain threshold in mice has been observed up to 4 h after p.o. administration of 0.02 mmol/kg of the prodrugs, when compared to the corresponding physical mixtures.



For chronic use of NSAIDs in certain conditions of neurodegenerative disorders molecular modifications of NSAIDs were planned. Galanakis *et al.* synthesized and evaluated amide derivatives of NSAIDs with *L*-cysteine ethyl ester [85]. The derivatives are reported to be potent antiinflammatory, antioxidant and hypocholesterolemic-hypolipidemic agents, with considerably reduced gastrointestinal toxicity. Doulgkeris *et al.* have designed and synthesized a series of novel molecules **42**, **43** having a residue of a classical NSAID (ibuprofen/indomethacin) and an antioxidant moiety, both attached through amide bonds to known nootropic structures like *l*-proline, *trans*-4-hydroxy-*l*-proline or *dl*-pipecolinic acid [86]. The compounds were found to retain anti-inflammatory and antioxidant activities, acquired hypocholesterolemic action, and possessed greatly reduced gastrointestinal toxicity.



With the goal of combining high antipyretic activity of paracetamol into commonly used NSAIDs, seven different NSAIDs were chemically combined with *p*-aminophenol to yield the p-amidophenol derivatives [87]. These were acetylated at the phenolic hydroxyl group to yield corresponding acetate derivatives for evaluating the impact of blocked phenolic hydroxy group on the biological activity of these derivatives. Only the *p*-amidophenol derivatives showed improved antipyretic activity over paracetamol with retention of anti-inflammatory activity and no ulcerogenicity.

It is well accepted that the mechanism of action of NSAIDs comprises of inhibition of cycloxygenase (COX) activity involved in the bisoxygenation of arachidonic acid to PGG_2 [88]. It was demonstrated that two pools of COX existed with vastly different sensitivities [89, 90] and finally it was discovered that COX-1 is a constitutive form expressed in platelets, kidneys and gastrointestinal tract [91, 92] and COX-2, the inducible isoform was found in elevated levels in the inflammatory exudates. These findings paved the way for search of selective COX-2 inhibitors. Since then many diarylheterocyclic compounds have been reported as selective COX-2 inhibitors [93, 94]. Few reports document structural modifications of conventional NSAIDs into selective COX-2 inhibitors. Certain ester and amide derivatives of indomethacin [95, 96], zomepirac [97], aspirin [98, 99] and flurbiprofen [100] have been reported to possess selective COX-2 inhibition. Reviewing of the developments in the field of selective COX-2 inhibitors is beyond the scope of this article.

NO RELEASING NSAIDS (NO-NSAIDS)

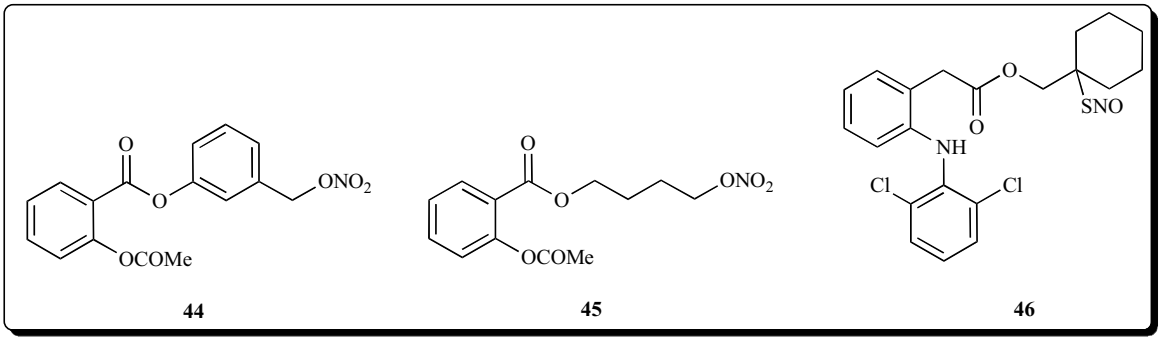
Another widely explored and promising approach towards the development of GIT-sparing NSAIDs is the linking of an NO releasing moiety to these compounds. The rationale behind developing this class of drugs is that, NO by maintaining gastric mucosal blood flow and preventing leucocyte adherence to the vascular endothelium of the splanchnic circulation (one of the earliest events following NSAID administration) may counteract the detrimental effect of COX-1 suppression so that mucosal injury does not occur [101].

The general structural features of NO–NSAIDs enable a large number of variations within the linking spacer and the NO-donating moiety. Owing to the ease of formation of these nitrate esters, several derivatives could be prepared for a given spacer. Till date, a significant amount of work on NO–NSAIDs and other related compounds has been reported [102].

These so called "NO-NSAIDs" (also known as cox inhibiting nitric oxide donors, CINODS) have been claimed to have comparable or superior antiinflammatory and analgesic activities in acute and chronic inflammation model in rat while, sparing the gastrointestinal tract and kidney of injury. Interestingly, NO-NSAIDs have been shown to accelerate the healing of pre-existing gastric ulcers [103] and restore renal function and structure in rats when subjected to renal ablation [104].

Two NO-releasing aspirins are 3-(nitroxymethyl)phenyl 2-acetoxybenzoate (NCX-4016) **44** and 4-nitroxybutyl 2-acetoxybenzoate (NCX-4215) **45**. NCX-4016, a stable compound otherwise, requires enzymatic hydrolysis to liberate NO at a constant rate. Following intragastric administration of NCX-4016, levels of NO are elevated both in gastric contents and plasma [105]. NCX-4016 was shown to possess greater anti-inflammatory and analgesic activities than aspirin [106, 107]. It also exhibited antithrombotic activity in several platelet dependent and independent animal models [108, 109]. NCX-4215 did not produce macroscopically visible histological damages in the rat stomach when administered up to 300 mg/kg, whereas 100 mg/kg aspirin produced widespread hemorrhagic damage [110, 111]. These protective effects were also seen in the stomach of aged rats treated with NCX-4016 [112]. NCX-4016 produced an equipotent inhibition of mucosal PGE_2 generation in the stomach when compared with aspirin [113].

The hypothesis that nitroaspirins could positively modulate changes in gastrointestinal damage was varified by testing the ability of NCX-4016 to prevent gastric damage in a rat model of shock [114]. Oral administration of NCX-4016 indicated the lack of gastric toxicity of NCX-4016, but not of aspirin, in the stomach of diabetic rats [115]. To improve upon efficacy of aspirin in hypertensive patients, Glimer *et al.* have reported synthesis and evaluation of isosorbide mononitrate derivatives of aspirin [116]. Isosorbide-5-mono-



nitrate-2-aspirinate (ISMNA) was found to be stable enough in hydrolysis studies to be absorbed intact from GIT and liberate nitric oxide in plasma to support GI mucosal integrity and augment aspirin's antiplatelet effects. S-Nitrosothiol esters of diclofenac e.g. **46** and other NSAIDs comprise a novel class of NO-donating compounds with anti-inflammatory and analgesic properties possessing a markedly enhanced gastric safety profile [117,118].

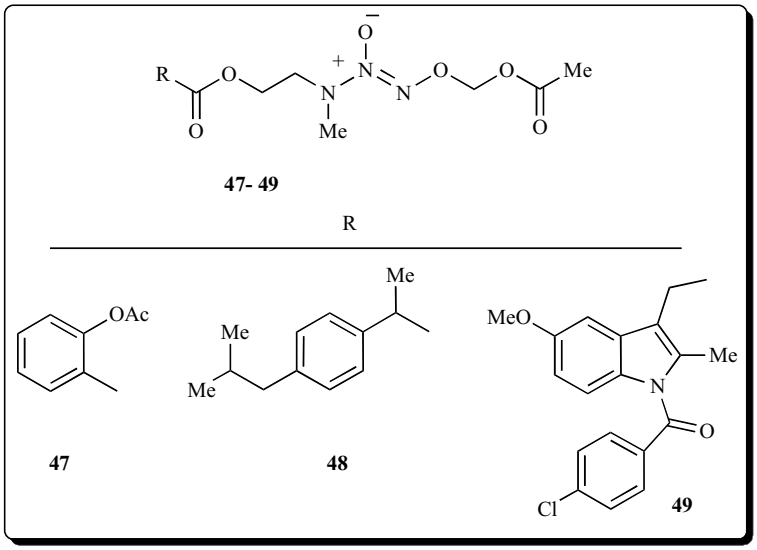
A range of standard NSAIDs, like naproxen, ibuprofen, flurbiprofen, ketoprofen and aspirin, have been coupled to NO-donating moieties and their actions extensively explored in a variety of experimental models over the past ten years demonstrating amply the efficacy, potency and spectrum of activity [119, 120].

Beneficial properties of NO-donating groups have been characterized in several animal models of upper and lower GI damage [121] by exerting local protective actions including mucosal vasodilatation and prevention of neutrophil adhesion in both the gastric and intestinal microcirculation and maintaining mucosal cell integrity [122]. Clinical studies on NO-naproxen, coded as AZD3582, supported the experimental findings demonstrating its effective anti-inflammatory and analgesic actions [121, 123].

Cena *et al.* reported a new series of NSAIDs in which aspirin was joined through an ester linkage to furoxan moieties, having the ability to release NO. All the products described presented a trend towards anti-inflammatory activity devoid of acute gastrotoxicity, principally due to their ester nature, and an antiplatelet activity due to their ability to release NO. But, they did not behave as aspirin prodrugs in human serum [124].

A novel group of hybrid NO-NSAIDs possessing a 1-(pyrrolidin-1-yl)diazen-1-ium-1,2-diolate or 1-(*N*,*N*-dimethylamino)diazen-1-ium-1,2-diolate moiety attached *via* methylene spacer to the carboxylic acid group of the traditional NSAIDs aspirin, ibuprofen, and indomethacin were reported by Vela´zquez *et al*. These prodrugs showed equipotent anti-inflammatory activities *in vivo* to that of the parent drugs aspirin, ibuprofen, and indomethacin [125]. Ester derivatives of aspirin, ibuprofen and indomethacin with O(2)-acetoxymethyl 1-[N-(2-hydroxyethyl-N-methylamino]diazenium diolate **47-49** were synthesized as NO-releasing prodrugs [126]. The derivatives did not exhibit *in vitro* COX inhibitory activity against COX-1 and COX-2 isozymes but significantly decreased carrageanan induced rat paw edema showing an enhanced *in vivo* anti-inflammatory activity relative to the parent NSAIDs. The *in vivo* ulcer index (UI) assay showed that aspirin derivative (UI = 0.8), ibuprofen derivatives (UI = 0) and indomethacin derivatives (UI = 1.3) were significantly less ulcerogenic when compared to the parent drugs, aspirin (UI = 57), ibuprofen (UI = 46) and indomethacin (UI = 34) at eqimolar doses.

A series of NO-donating N-subsituted glycolamides of naproxen have been reported to posses anti-inflammatory



activity in rat carrageenan paw edema model [127]. Ibuprofen esterified with NO donor moiety abolished GI irritation and significantly reduced thinning with no alteration in levels of diaphorase [128].

NO-donating prodrug of naproxen, NMI-1182 and AZD3582, are reported to produce significantly lesser gastric lesions after oral administration than naproxen [129]. NCX-530, an NO releasing derivativ of indomethacin has been reported to decrease gastric motility, increased mucosal blood flow and caused a marked inhibition of PGE_2 formation in intact and ulcerated gastric mucosa [130].

Data from several laboratories indicate that NO-NSAIDs could be effective in a variety of diseases including cardiovascular, rheumatological, lung and Alzheimer's diseases, and cancer [131-134].

Hydrogen sulphide was observed to exert anti-inflammatory and analgesic activity. It is also reported to be a vasodilator and suppressor of leukocyte adherence to vascular endothelium. Fiorucci *et al.* have reported that inhibition of hydrogen sulfide generation contributes to gastric injury caused by anti-inflammatory nonsteroidal drugs [135]. Based on these findings various ester derivatives of clinically used NSAIDs namely ibuprofen, naproxen, diclofenac, indomethacin, ketoprofen and aspirin with various hydrogen sulphide releasing moieties (4-thiocarbamoylphenol, 5-[4-hdroxyphenyl]-1,2-dithiole-3-thione) have been reported [136]. These derivatives have been reported to show significantly less gastric injury than the NSAID alone.

Reduced mucosal prostaglandin (PG) levels, increased gastric acidity and increased gastric motility are reported to be important causes for the NSAIDs induced gastropathy. The increased gastric motility leads to a reduced mucosal blood flow, hypoxia and destruction of the mucous bicarbonate barrier, which prevents back diffusion of pepsin and hydrogen ions from lumen into the mucosal layer. Microcirculation in gastroduodenal mucosa supplies energy and oxygen to mucosal cells, removes hydrogen ions, waste products, and transports bicarbonate to the surface of the gastric epithelium. This way, the mucosal blood flow plays a very crucial role in supporting the defense mechanism of mucosa [137]. Based on these reports an attempt was made to incorporate anticholinergic activity into the basic molecules of conventional NSAIDs (flurbiprofen, biphenylacetic acid, naproxen, 6-methoxynapthylacetic acid, diclofenac, aspirin and ketorolac) by derivatizing them into N,N-disubstituted aminoalcohol esters. These derivatives were designed specifically to resemble the aminoalcohol ester class of anticholinergics [138-143]. An entirely new pharmacodynamic property was incorporated into the original NSAIDs molecules with the anticipation that besides preventing local GI irritation by temporarily blocking carboxyl group present in the NSAIDs, the introduction of anticholinergic activity in the intact esters would further aid in reducing the GI toxicity by (i) decreasing gastric acid secretion and (ii) decreasing gastric motility to maintain optimal mucosal blood flow. Most of the aminoalcohol esters were found to undergo fast enzymatic cleavage in 80 % human plasma and possessed anti-inflammatory activity comparable to the respective parent drugs in carrageenan induced rat paw edema model. A significant reduction in ulcerogenic potency in comparison to the parent drugs with a slightly higher anti-inflammatory potency suggests that majority of these candidates have an improved therapeutic profile over their parent drugs.

CONCLUSIONS

Inspite of extensive efforts in the direction of separation of therapeutic effect of NSAIDs from their GI toxicity, the search for an ideal prodrug with a superior therapeutic advantage for clinical use still remains unmet. Further, research is needed to design and identify prodrugs, which would be appropriate for clinical use in terms of stability, metabolism, toxicology and side effects.

Instead of synthesizing new compounds which is a time consuming and too costly an affair, the designing of derivatives of existing clinically used NSAIDs is definitely an interesting and promising area of research. Moreover, as the metabolic profile of the liberated parent drug (after cleavage of the derivative in the body) would be already known, it could be advantageous to design derivatives of parent NSAIDs.

Synthesis of prodrugs of NSAIDs is not only an effective way of overcoming the GI toxicity but could also be used for combining other pharmacological properties or incorporating a chemical moiety for an added beneficial effect (like development of NO-NSAIDs [103, 104], conjugation with H_2 receptor antagonist [75] or an analgesic agent [87] and incorporating anticholinergic activity for reducing gastric acid secretion [138-143].

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