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A perspective review on role of novel NSAID prodrugs in the management of acute inflammation

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ABSTRACT

Inflammation mediators, prostaglandins are causing inflammation, pain and pyrexia in the body. Synthesis of these mediators can be effectively blocked by administering the non-steroidal anti-inflammatory drugs (NSAIDs). The NSAIDs had age-old history in medicine due to their therapeutic potentials and thus they occupy the major share in clinical practice as well as in commercial market. Mostly the NSAID moieties are chemically composed of carboxylic functional groups and this could be a potential reason for the damage of mucosal lining. Moderate and chronic oral use of these NSAIDs leads to ulcerogenicity, abdominal cramps, intestinal bleeding, mucosal haemorrhage and gastritis. Therapeutic handling of above side-effects is becoming ever challenge for the researchers. In research of surmounting side-effects caused by NSAID, prodrug approach was proven to be effective and successful. Over the time, prodrug concept becomes big boom in the arena of inflammation and its clinical treatment. In last few decades, many researchers have been attempted to synthesize the NSAID prodrugs successively. With this background of information, this article was composed and aimed to provide needful information on NSAID prodrugs such as background history, rationale, mechanism of action, principles involved and their therapeutic outcomes. The successful prodrugs were listed and their molecular structures were also demonstrated here.

1. Introduction

1.1. Prodrugs

They are bioreversible derivatives of pharmacologically active agents that must undergo an enzymatic and/or chemical transformation *in vivo* to release the parent drug, which can then elicit its desired pharmacological effect[1,2]. The schematic representation of prodrug was shown in Figure 1.

"Bioprecursors" are prodrugs which lack promoiety but result from a molecular modification of the active drug itself *in vivo*. Co-drugs are prodrugs which contain two pharmacologically active drugs that are combined together in a single molecule, so that each drug acts as a carrier for the other[3].

1.1.1. Rationale of prodrugs

Drug discovery is expanding rapidly in the 21st century by employing various techniques like combinatorial chemistry, high throughput screening and receptor-based drug design. By using these technologies, new molecular moieties were identified but their physicochemical and biopharmaceutical aspects were ignored. This eventually led to poor drug-like properties and high failure rate in drug development despite its high demand[4]. Thus, prodrug process was initiated with major objective of optimization of absorption, distribution, metabolism, excretion and toxicity properties which are expected to increase the efficacies. Prodrug is an exciting area of research that can be applied to all drug moieties whose pharmacological response is limited. This resulted in the increased number of approved prodrugs in the market[1,5,6].

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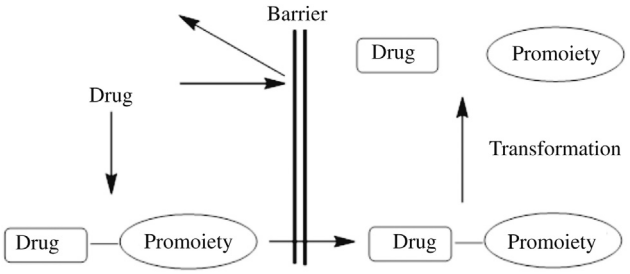


Figure 1. Schematic representation of prodrug and its metabolism.

1.1.2. History of prodrugs

The term prodrug was first coined in the year 1958 by Albert to describe compounds which undergo biotransformation prior to their pharmacological response[7]. Simultaneously in the same year Harper introduced the term drug latentiation.

Methenamine, the first prodrug was introduced in the year 1899 by Schering as site-activated prodrug because of its conversion to formaldehyde at the acidic urine pH (Figure 2).

In the same year, aspirin was introduced which hydrolyses to salicylic acid and acetate. Acetate ion causes irreversible inactivation of cyclooxygenase (COX) by binding to the serine residue on the active site of COX enzyme and results in the suppression of production of prostaglandins and thromboxane is displayed in Figure 3[8]. Prontosil, an anti-inflammatory agent was the prodrug of sulphanilamide (first sulpha drug) (Figure 4).

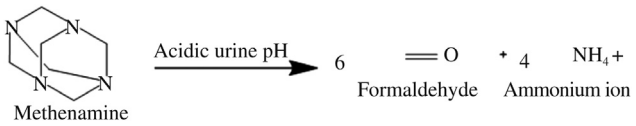


Figure 2. Metabolism of methenamine.

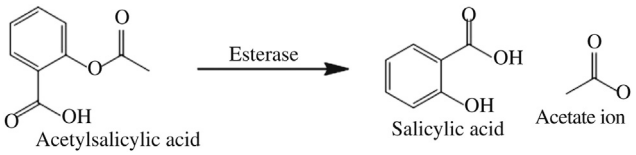


Figure 3. Metabolism of acetylsalicylic acid (aspirin).

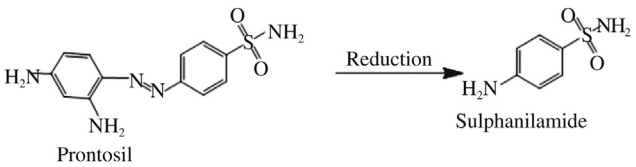


Figure 4. Metabolism of prontosil.

Very popular non-steroidal anti-inflammatory drug (NSAID) prodrug is paracetamol which metabolises to *p*-aminophenol. *p*-Aminophenol reacts with arachidonic acid and forms *N*-arachidonoyl-phenolamine thus eliciting its analgesic effect. The unintentional prodrugs of paracetamol: acetanilide (1886) and phenacetin (1887) were the first aniline derivatives but their therapeutic efficacy was discovered later, via the common metabolite of paracetamol (Figure 5)[9].

Prodrug approach is the best approach to circumvent the problems associated with formulation, administration, absorption, distribution, metabolism, excretion, toxicity and life cycle management[10].

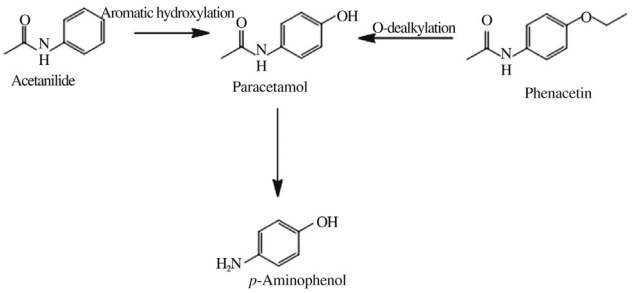


Figure 5. Metabolism of paracetamol.

The article is embodied with various numbers of prodrugs of NSAID category, promoieties used in their preparation, schematic evaluation with preclinical and clinical outcomes. This review article also emphasizes on the current status of prodrugs of above said category with their retrospective aspects as follows.

1.2. NSAIDs

In ancient Asia, China and Egypt, several plants containing salicylic acid and its constituents were used to treat fever and to relieve the pain of rheumatism and child birth. In 1763, Edward Stone published the use of willow bark to reduce fever. Later in 1860, salicylic acid was synthesized in the laboratory to treat rheumatism, and as antipyretic and external antiseptic agent. It was surprised that salicylic acid had extraordinary bitterness which limited the patient's compliance. To make it palatable, Flex synthesized acetylsalicylic acid or aspirin in 1899 and suggested that aspirin liberates salicylic acid to elicit its anti-inflammatory action. So aspirin acts as a prodrug. Progressively, several drugs which share the same action of aspirin were discovered such as phenacetin, antipyrine, phenylbutazone, acetaminophen, indomethacin, naproxen and ibuprofen and they are known as “aspirin-like drugs”. Over time, these drugs were noted as “NSAIDs” as they were distinct from glucocorticosteroids[11].

Prostaglandins produced via COX pathway, which are major physiological and pathological mediators in inflammation, pain, pyrexia, cancer and neurological diseases (Figure 6). Biomembrane bound arachidonate is converted to free arachidonic acid by phospholipase A_2. In this COX pathway, the two known COX isoforms: COX-1 and COX-2 convert the arachidonic acid to prostaglandin G_2 which further undergoes reduction in the presence of peroxidase to form PGH_2. This PGH_2 is converted to PGD_2, PGE_2, PGI_2, PGF_2 and thromboxane A_2. COX-1 is expressed in most tissues and the prostanoids produced by this isoform mediate functions such as regulation of renal blood flow, cytoprotection of the gastric mucosa and platelet aggregation. COX-2 is expressed in brain, spinal cord and kidneys. It is an immediate early response gene highly restricted under basal conditions but highly inducible in response to inflammatory stimuli, including endotoxin, cytokines, hormones and tumour promoters.

Blocking the COX enzyme results in the reduction of synthesis of prostaglandins, which leads to decrease in inflammation (due to decrease of PGE_2 and PGI_2), pain and fever. The inhibition of prostaglandins leads to wide range of side effects, which includes gastrointestinal (GI) irritation, cardiovascular effects, renal toxicity, exacerbation of hypertension and fluid retention. Non-selective NSAIDs cause GI ulceration and

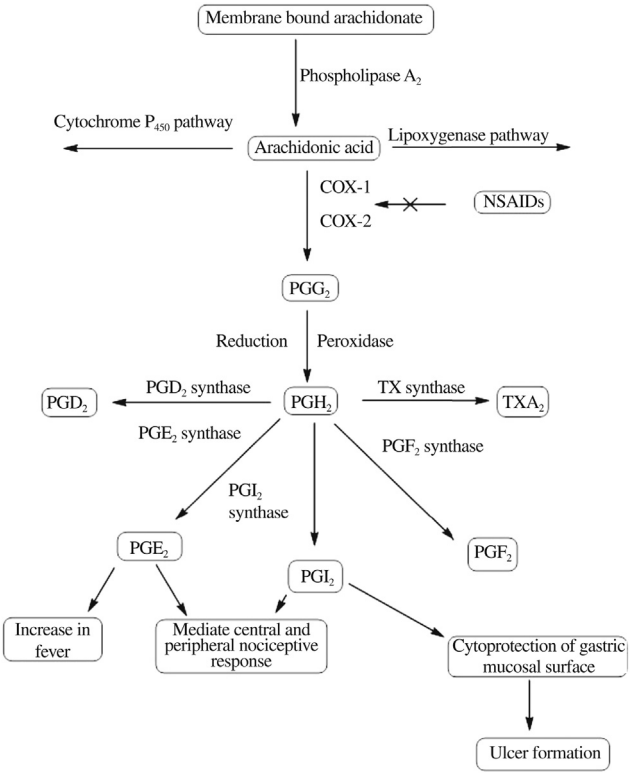


Figure 6. Mechanism of action of NSAIDs.
PGG_2: Prostaglandin G_2; PGH_2: Prostaglandin H_2; PGD_2: Prostaglandin D_2; PGE_2: Prostaglandin E_2; PGI_2: Prostaglandin I_2; TXA_2: Thromboxane A_2; PGF_2: Prostaglandin F_2.

potentially upper GI perforation and bleeding because they inhibit not only COX-2 but also COX-1. GI mucosal injury produced by NSAIDs is caused by two mechanisms. The first mechanism involves direct contact which leads to local irritation by carboxylic group of NSAIDs and local inhibition of prostaglandin synthesis in the GI tract. The other principle was due to an ion trapping mechanism of NSAIDs from the lumen into the mucosa. The development of COX-2 selective inhibitors offered same efficacy without GI toxicity but caused greater risk of increased serum potassium levels and potential liver toxicity[12,13].

NSAIDs show undesirable physicochemical properties as explained above and their therapeutic efficacy can be improved by prodrug approach. NSAIDs were converted to ester or amide mutual prodrugs which prevent direct contact of the parent drug with the gastric mucosal lining in the GI tract, with improved physicochemical properties and enhanced bioavailability.

Below listed NSAID moieties have scrupulously designed into effective and potential prodrugs for clinical use, explained chronologically here.

1.3. Aceclofenac

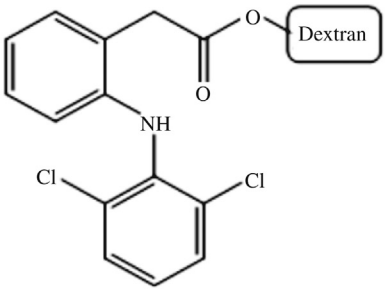
Aceclofenac exerts pharmacological effect by predominantly suppressing the proinflammatory cytokine synthesis[14]. Thus, it becomes a potential candidate in class of NSAID category. But, its chronic oral use leads to severe ulcerogenicity. In circumventing of ulcerogenicity, one of the approaches was the synthesis of aceclofenac prodrugs. Aceclofenac was conjugated with macromolecules such as dextran 10 000 and 20 000. Resulted prodrugs were reported with increased anti-inflammatory efficacies without ulcerogenicity[15]. On other hand, amino acids such as alanine, leucine, valine and proline were used to conjugate the aceclofenac with expected outcome of increased solubility, stability at acidic pH and hydrolysis at pH 7.4[16]. To overcome the pharmaceutical problem, aceclofenac was conjugated with phenylalanine using *N*, *N*′-dicyclohexylcarbodiimide which resulted in enhanced solubility and lipophilicity[17]. The mutual prodrugs of aceclofenac was synthesized by coupling method using various natural antioxidants such as menthol, thymol, eugenol, guaiacol and vanillin which showed improved pharmacological activity[18]. The molecular structures of aceclofenac prodrugs were displayed in Figure 7.

1.4. 5-Amino salicylic acid (ASA)

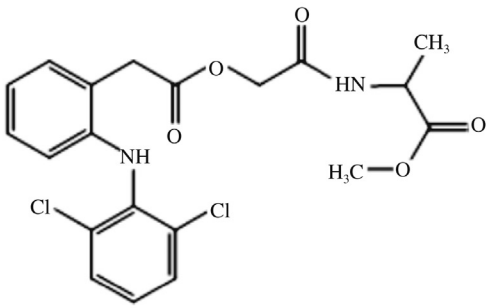
ASA is widely used in the treatment of ulcerative colitis. ASA is an active scavenger of released free oxygen radicals and inhibits prostaglandin synthesis[19]. Since it inhibits the prostaglandin synthesis, it can lead to damage of gastric mucosal layer. In order to overcome this problem, colon specific drug delivery of ASA was proposed. In this process, ASA was converted to mutual azo prodrug by coupling with L-tyrosine[20], azo dextran polymeric conjugate using *p*-amino benzoic acid and benzoic acid as linkers[21], acrylic-type polymeric prodrugs using methacryloyloxyethyl 5-aminosalicylate and *N*-methacryloylamidoethyl 5-aminosalicylamide[22] and pro-prodrug of 5-amino salicylic acid using L-lysine containing *trans*-ferulic acid[23]. Chemical structures were given in Figure 8.

1.5. Aspirin

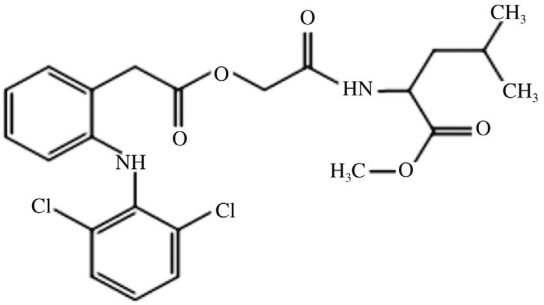
Aspirin exerts its effects by the inhibition of COX by the irreversible acetylation of serine functions with serious outcomes such as gastric ulcers, renal failure and impaired platelet function[24]. But still aspirin can be continued as an effective NSAID with relative safety by modifying it into prodrug. Aspirin prodrugs are reported in several research outcomes *e.g.* 1,3-bis(alkanoyl)-2-(*O*-acetylsalicyloyl)glycerides (aspirin triglycerides) were processed with reduced gastric lesions[25]; 1,3-dialkanoyl-2-(2-methyl-4-oxo-1,3-benzodioxan-2yl)glycerides (cyclic aspirin triglycerides) were also synthesized with same objective[26]. Later on few novel activated ester type prodrugs of aspirin such as methylthiomethyl, methylsulfinylmethyl and methylsulfonylmethyl esters were screened and among them methylsulfinylmethyl ester was found as promising prodrug[27]. Aspirin prodrug process was involved by complex kinetics and hydrolysis mechanisms *viz.* methylthiomethyl esters hydrolysed via a unimolecular alkyl-oxygen cleavage whereas methylsulfinylmethyl and (methylsulfonyl)methyl 2-acetoxybenzoate undergo neutral hydrolysis[28]. A series of glycolamide, glycolate, (acloxy)methyl, alkyl and aryl esters have exhibited solubility, lipophilicity and shelf-life[29]. On other case, 2-(2,6-dimethoxybenzyloxy)-2-methyl-4H-1,3-benzodioxin-4-one showed its promised prodrug activity[30]. Series of 2-substituted 2-methyl-4H-1,3-benzodioxin-4-ones were synthesized for significant keratolytic activity with pseudo first order[31]. A well stable isosorbide diaspirate ester moiety had surprisingly hydrolysed in human plasma[32]. Nitroaspirin also possessed aqueous stability and



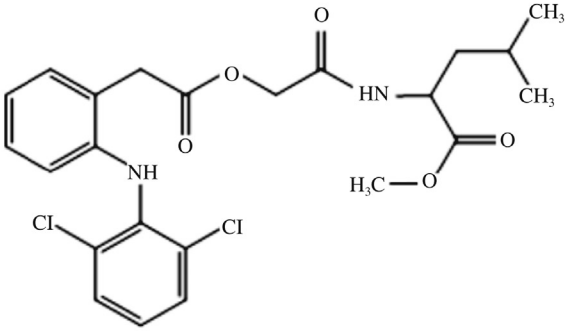
Aceclofenac dextran prodrug



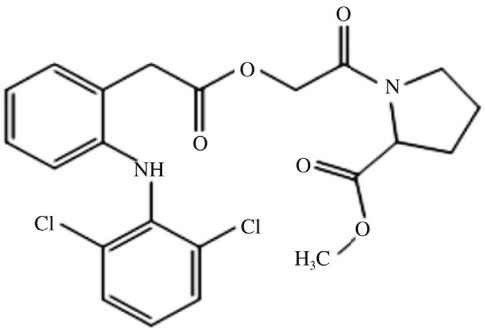
Aceclofenac alanine methyl ester



Aceclofenac leucine methyl ester



Aceclofenac valine methyl ester



Aceclofenac proline methyl ester

Figure 7. Prodrugs of aceclofenac.

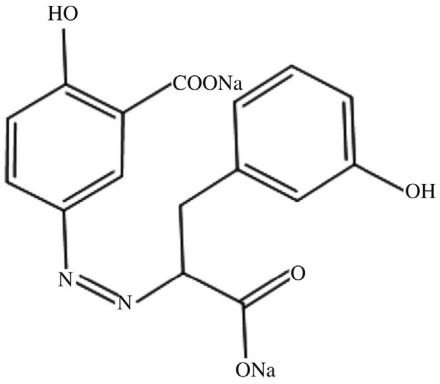
superior percutaneous absorption[33]. Pursuant, isosorbide-2-aspirinate-5-salicylate has portrayed plasma mediated hydrolysis with selective COX-1 inhibition devoid of gastric ulcers[34]. Potential antiplatelet activity was noticed from an ester linked furoxan moiety which is devoid of gastric lesions due to its differential ability in NO release[35]. Alkyl chains containing a nitroxy group (benzoyloxy)methyl esters were found to be stable in acidic pH environment but immediately metabolised by esterase and inhibited collagen induced platelet aggregation as well[36]. High pharmacokinetic profile of aspirin was achieved in colon specific and sustained release with dextran conjugation[37]. Increased permeation of methylsulfinylmethyl 2-acetoxybenzoate through depilated mice skin with simultaneous hydrolysis[38] was tabled. The structures of aspirin prodrugs were shown in Figure 9.

1.6. Dexibuprofen

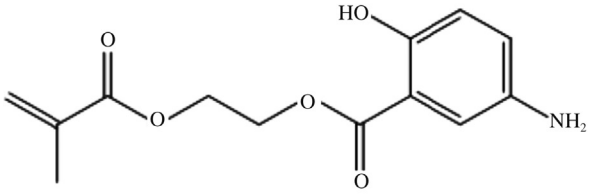
Oral administration of dexibuprofen has more patient compliance which can effectively inhibit both COX-1 and COX-2 enzymes in the treatment/management of inflammation and pain. Chronic oral use otherwise leads to serious GI complications and those can be minimised by macromolecular prodrugs[24]. Prodrugs processed by conjugating with polymers like dextran 10000 and 20000 and promising activity was outreached[39]. Similar kind of research was carried out on dexibuprofen conjugation with amino acids such as L-tryptophan, L-phenylalanine, L-glycine and L-tyrosine[40]. Brain targeted delivery systems were successfully developed with objective of enhanced distribution by ethanolamine prodrugs[41]. The prodrugs were illustrated in Figure 10.

1.7. Diclofenac

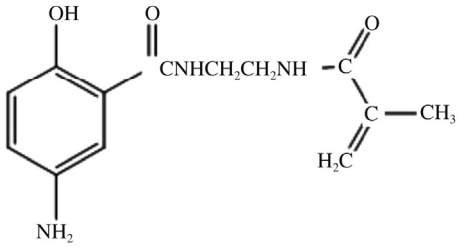
Diclofenac inhibits the synthesis of substance P, a proinflammatory neuropeptide and nociceptive prostaglandins in synovial tissue and blood. But its clinical use is restricted due to GI haemorrhage[42]. In order to overcome GI haemorrhage, diclofenac prodrugs were synthesized using iodomethyl pivalate, 1-iodomethyl isopropyl carbonate and 2-acetoxyethyl bromide as conjugates which exhibited more lipophilicity with partition coefficient 3 and showed reduced ulcerogenicity[43]. Similar outcome resulted from diclofenac prodrug containing 1-(2,6-dichlorophenyl)indolin-2-one as the promoiety with decreased



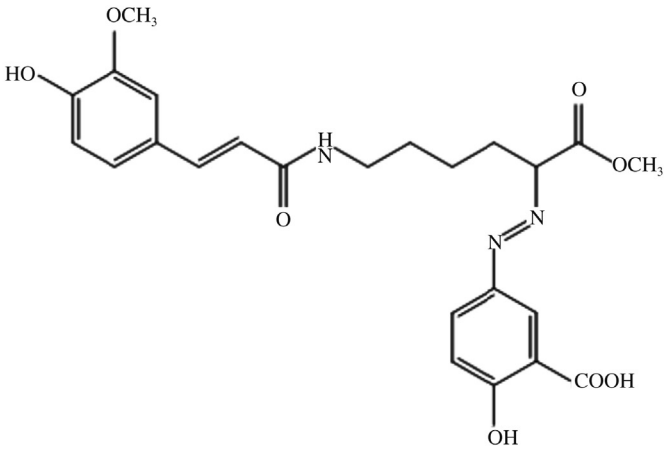
Azo conjugate of ASA with tyrosine



Methacryloyloxyethyl 5-aminosalicylate



N-methacryloylamidoethyl 5-aminosalicylamide



ASA pro-prodrug

Figure 8. Prodrugs of ASA.

PGE_2 levels and COX-2 expression[44]. A series of prodrugs containing methanol, diclofenac ester, glycol, glycerol and 1,3-propylene glycol have displayed their potentials in transdermal delivery with better fluxes[45]. It was noticed that diclofenac constituted as promising depot with long acting [2-(1-methyl-1H-imidazol-2-yl)ethyl ester of diclofenac][46]. The prodrugs were demonstrated in Figure 11.

1.8. Diflunisal

Diflunisal inhibits uncoupling oxidative phosphorylation which inhibits mitochondrial ATP synthesis thereby inhibiting prostaglandin synthesis[47]. Oral use causes peptic ulceration, GI bleeding and perforation. Acetyldiflunisal (Figure 12), a human serum albumin based prodrug has disclosed two fold weak binding affinity *i.e.* more easily released into the circulation[48].

1.9. Etodolac

Etodolac is a potent anti-inflammatory agent, which acts by inhibiting interleukin-1beta induced PGE_2 biosynthesis in chondrocytes, active oxygen generation and bradykinin formation[49]. This mechanism eventually ended up with ulcerogenicity, which was surmounted by macromolecular prodrugs by conjugating the drug with high molecular weight polymers such as dextran 40000, 60000, 110000 and 200000[50] and with dextran 10000 and 20000[51]. In another instance, mutual amide prodrug of etodolac with glucosamine has shown synergistic effect, increased solubility and sustained release profiles[52]. Figure 13 displays the prodrugs of etodolac.

1.10. Fenoprofen

Fenoprofen is a potent inhibitor of PGE_2 synthesis[53]. It also damages the epithelial lining of gastric mucosa in chronic oral use. With this context, fenoprofen was designed into polymer conjugated prodrug. The prodrugs differed in covalent bonding, type and/or length of spacer and drug loading[54]. Poly [alpha,beta-(*N*-2-hydroxyethyl-DL-aspartamide)] (PHEA)-fenoprofen prodrug was conjugated by covalently binding fenoprofen to poly[α,β-(*N*-2-hydroxyethyl-DL-aspartamide)] and evaluated for kinetics[55]. The prodrugs were drawn in Figure 14.

1.11. Flufenamic acid

The mechanism of action of flufenamic acid was the activation of AMP-activated protein kinase through Ca^{2+}/calmodulin-dependent kinase–kinase pathway[56]. With above mechanism, the drug candidate has emerged as a potent NSAID and also posed the gastric complications. In order to lower the side-effects of oral use of flufenamic acid, dextran conjugated prodrug was synthesized with aim of colon specific delivery[57]. A breakthrough on nanoprodrugs of flufenamic was coined recently[58]. Structures of these prodrugs were represented with Figure 15.

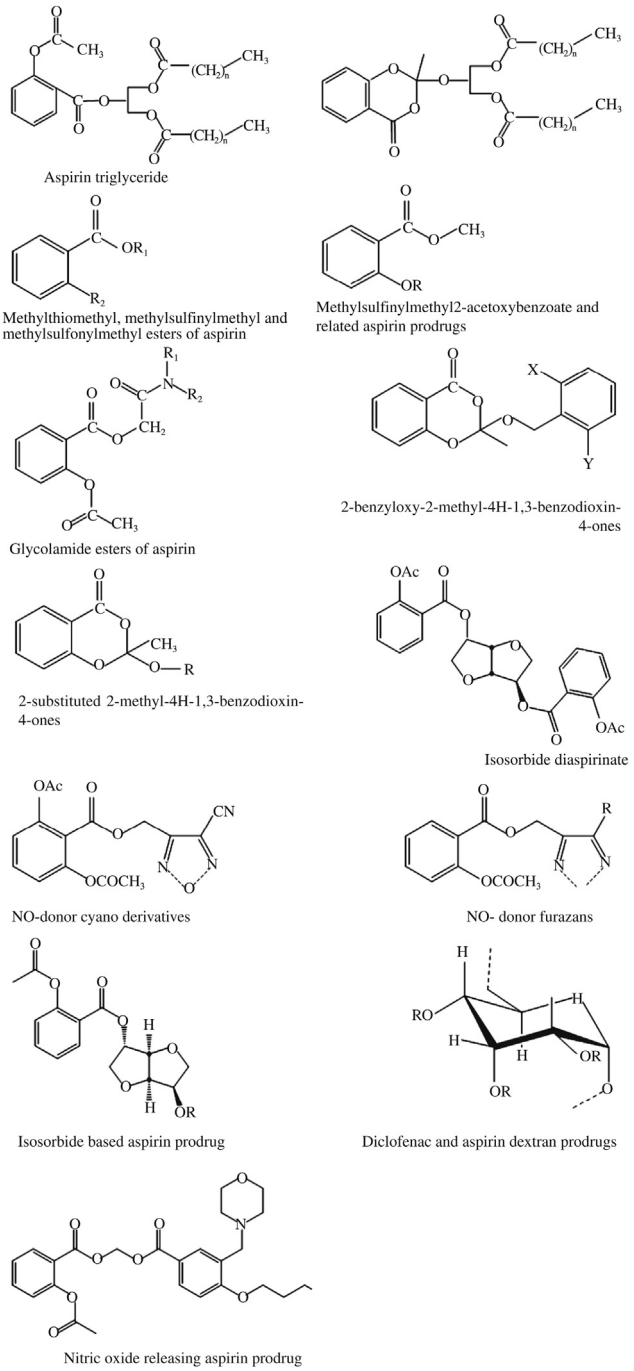


Figure 9. Prodrugs of aspirin.

1.12. Flurbiprofen

Flurbiprofen inhibits both COX enzymes effectively[59]. Prolonged oral use of this drug is adversely reported with gastric lesions and inflammation at epithelial lining. In order to circumvent above problems, sustained release of flurbiprofen was racked up by amino acid ethyl esters using L-arginine, L-lysine and L-phenylalanine[60]. Amide conjugates of flurbiprofen with various amino acid methyl esters synthesized by Schotten-Baumann method showed increased aqueous solubility, significant activity with reduced ulceration[61]; dextran prodrugs by conjugating *N*-acyl imidazole derivative of flurbiprofen and suprofen with dextran 40000, 60000 and 110000 also displayed the same good results[62]. Increased hydrophilicity, less ulcerotoxicity and colon specificity were achieved by coupling flurbiprofen with L-glycine to form an amide prodrug[63]. Flurbiprofen for transdermal delivery using proniosomes as carrier was tabled in recent past[64]. Novel emulsion of flurbiprofen axetil was prepared by high pressure homogenization using Tween 80 as an emulsifier and the results proved that it was a promising formulation for ophthalmic anti-inflammatory activity[65]. Lipid nanocarriers containing ester prodrugs of flurbiprofen using pegylated nanostructured lipid carriers were processed for parenteral administration[66]. The prodrugs were elucidated in Figure 16.

1.13. Ibuprofen

Ibuprofen, a racemate undergoes unidirectional metabolic chiral inversion of the R-enantiomer to the S-form which inhibits both COX-1 and 2[24,51]. Thus, it causes gastric erosions. Ibuprofen was esterified with glycolamide along with unsubstituted carriers such as *N*,*N*-dimethyl and *N*,*N*-diethyl in order to address the above gastric repercussions of ibuprofen oral use[67]. Reduction of GI disturbances was evidently accomplished by ibuprofen and diclofenac with glucosamine as mutual prodrug[68], glyceride prodrugs of ibuprofen with 1,2,3-trihydroxy propane 1,3-dipalmitate/stearate[69], glucopyranoside–ibuprofen conjugates using α-methyl, ethyl and propyl glucopyranoside[70], conjugating ibuprofen with dextran 10000 and 20000[71]. Controlled release was substantiated by a novel acrylic type polymer, methacryloyloxy(2-hydroxy)propyl-4-isobutyl-α-methylphenyl acetate[72]. Anhydride prodrug of ibuprofen used polyacrylic acid based polymers[73]; polyethylene glycol conjugates have proven their chemical stability in aqueous buffer[74]. A novel series of rhein NSAID prodrugs containing anthraquinone by linking rhein through glycol ester to ibuprofen, aspirin, naproxen, indomethacin and diclofenac[75] were synthesized. Ibuprofen-polyethylene glycol (PEG) derivatives synthesized by esterification of substituted PEGs such as hydroxy ethyl ester, hydroxy ethylamide and hydroxy ethyl, were susceptible towards hydrolysis[22]. Novel ibuprofen prodrug for parenteral administration was successfully designed with 3-hydroxy butyric acid oligomers[76]. Later on, xylan based ibuprofen nanoparticles as prodrugs attained superiority due to its reduced size and stability towards hydrolysis[77,78]. Important chemical structures of ibuprofen prodrugs were given in Figure 17.

1.14. Indomethacin

Indomethacin has time dependent tight binding effect on COX-1 and 2[77,78]. Thus, it causes ulcerations at GI mucosa. Potential ulcerotoxicity of indomethacin was successfully addressed by prodrugs of indomethacin such as mono-, bis- and tris [1-(*p*-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetyl] glycerides and 1,3-dialkanoyl-2-[1-(*p*-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetyl]glycerides. These prodrugs also exhibited anti-oedema effects. Similar successes were continued with apyramide, an ester of indomethacin and acetaminophen[79] and also with 3-(*N*,*N*-diethylamino)propylindomethacin HCl[80]. Prodrugs were conjugated with triethylene glycol ether linkage with aim of rapid hydrolysis whereas amide conjugates aimed for pH independent stability[81]. Later on a peroral controlled

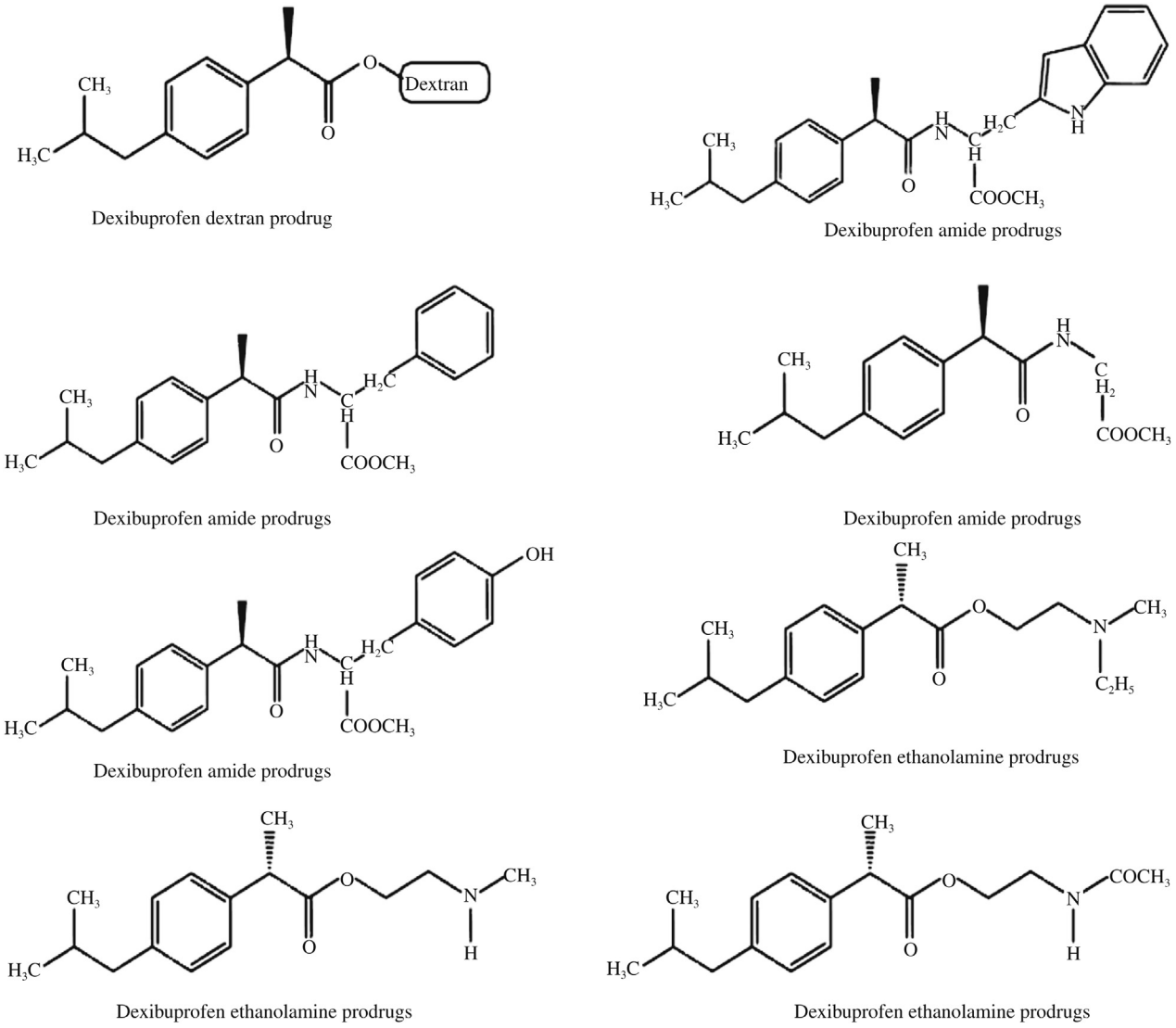


Figure 10. Prodrugs of dexibuprofen.

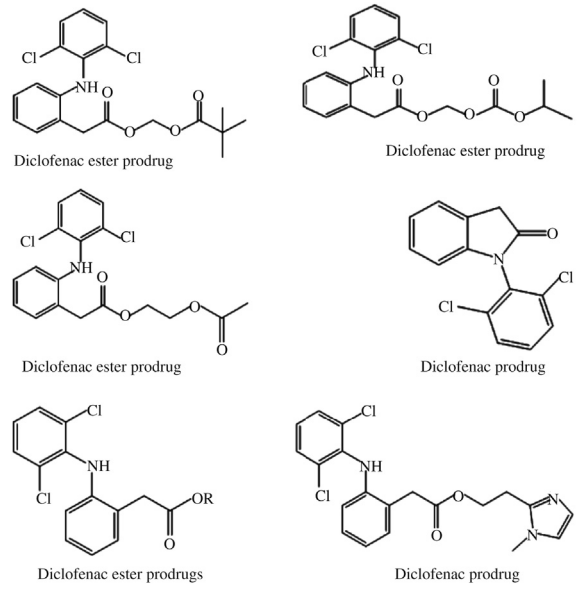


Figure 11. Prodrugs of diclofenac.

release of indomethacin–lecithin conjugate was figured out[82] and sequentially interfacial deposition model was adopted to prepare indomethacin ethyl ester-loaded nanocapsules[83]. Further, prodrug moieties synthesized by linking 1-iodomethyl pivalate, 1-iodoethyl isopropyl carbonate, 2-bromoethyl acetate and 4-chloromethyl-5-methyl-1,3-dioxol-2-one through esterification to address the ulcer toxicities[84]. Structures of designed prodrugs were provided in Figure 18.

1.15. Ketoprofen

Ketoprofen has the ability to activate serotonergic mechanism and release 5-hydroxytryptamine along with inhibition of prostaglandins at the central level[85]. Thus, it has supremacy over other NSAIDs. But it is known to have a severe side-effect on GI mucosal lining. Prodrug approach was figured out to address the potential side-effect. In doing so, it was attempted on 1-alkylazacycloalkan-2-one esters[86] and ketoprofen-PEG by esterification and by conjugating niacin and ketoprofen with bile acid chenodeoxycholic acid using lysine as a linker[87]. Resulted prodrug had lipophilicity and demonstrated sustained release from topical administration. They were reported with their chemical structures in Figure 19.

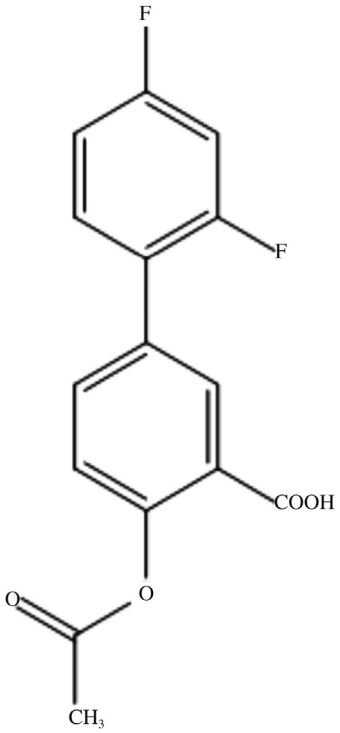
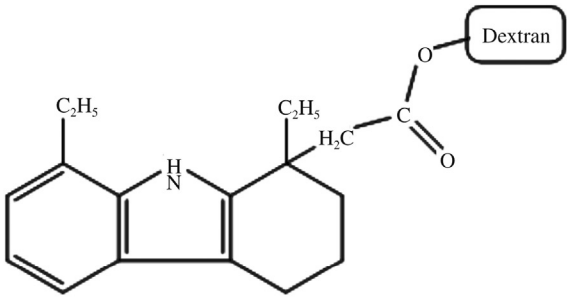


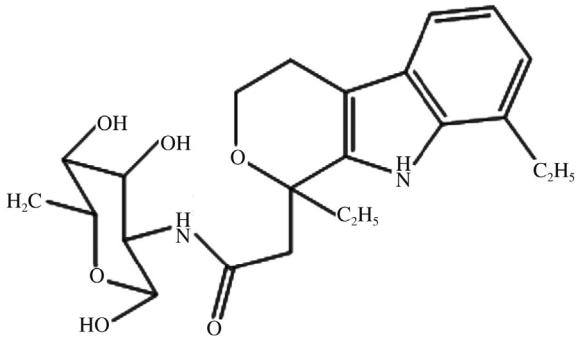
Figure 12. Prodrug of diflunisal.

1.16. Ketorolac

Ketorolac inhibits prostaglandin synthesis and also activates NO-cyclic GMP-ATP-sensitive K^+ channel pathway which results in peripheral antinociceptive effect[88]. It was reported to have gastric ulcerations upon administration and instability over topical administration due to enzymatic effects. These issues were addressed with ketorolac amide prodrugs[89]. Fatty esters such as decenoate, dodecanoate and palmitoleate were used to conjugate ketorolac for more enzymatic stability in skin during permeation[90]. In this advancement, piperazinyl alkyl esters possessed higher permeation at various pH conditions[91]. Prodrugs with tertiary butyl and benzyl esters demonstrated higher fluxes; ester prodrugs with heptyl and diketorolac heptyl exhibited sustained release with selective absorption and greater follicular uptake[92]. Pharmacokinetics of pentyl ester[93], 6-aminoethyl and amino butyl esters of ketorolac containing 1-methyl piperazine, *N*-acetyl piperazine and morphine[94] followed pseudo first-order. Gastric toxicities were addressed by macromolecular prodrugs with dextran 40000, 60000, 110000 and 200000[95]. Principle of reversible conjugation to D-galactose[96] and ethyl esters of amino acids glycine, phenylalanine, tryptophan, L-valine, isoleucine, L-alanine, leucine, glutamic acid, aspartic acid and β-alanine were applied for sustained release purpose and to address the

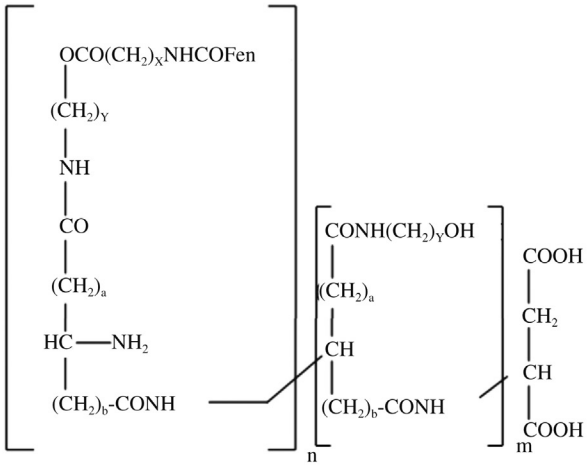


Etodolac dextran prodrug

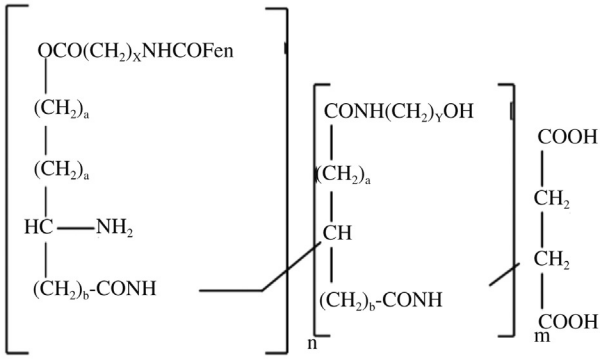


Mutual amide prodrug of etodolac-glucosamine

Figure 13. Prodrugs of etodolac.

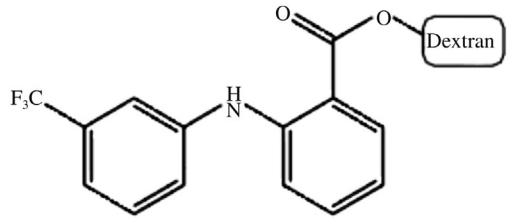


Polyhydroxy aspartamide polymer prodrugs

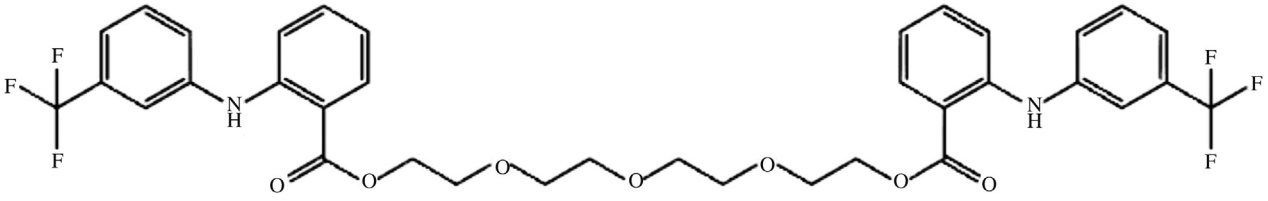


PHEA-fenoprofen prodrug

Figure 14. Prodrugs of fenoprofen.

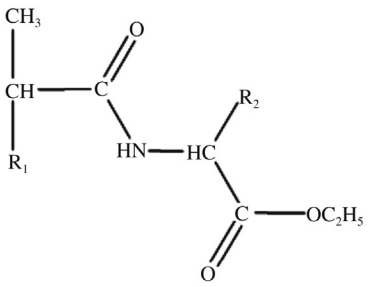


Flufenamic acid dextran prodrug

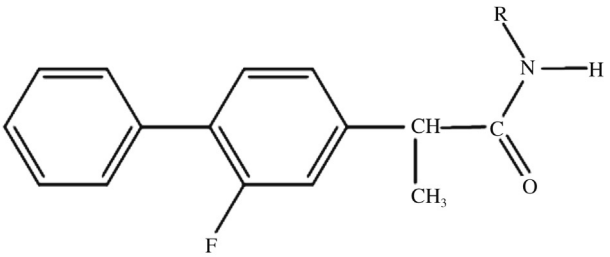


Flufenamic acid tetraethylene glycol prodrug

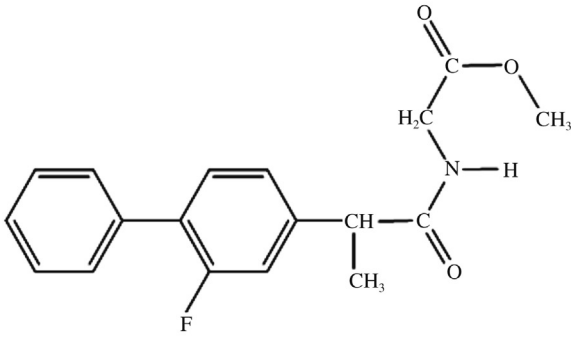
Figure 15. Prodrugs of flufenamic acid.



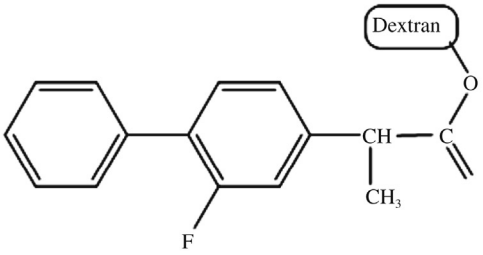
Flurbiprofen ethyl esters of L-arginine, L-lysine and L-phenylalanine



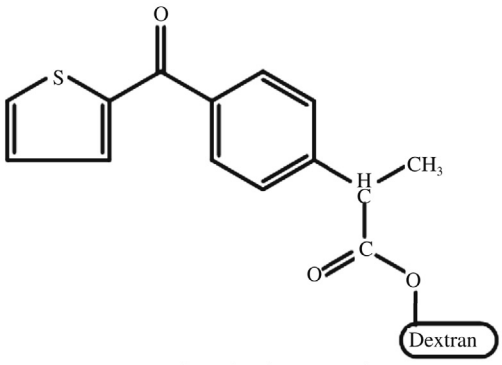
Flurbiprofen amide conjugates



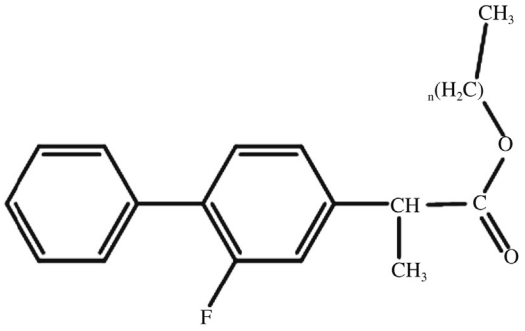
Flurbiprofen glycine conjugate



Flurbiprofen dextran prodrug



Suprofen dextran prodrugs



Flurbiprofen ester prodrugs

Figure 16. Prodrugs of flurbiprofen.

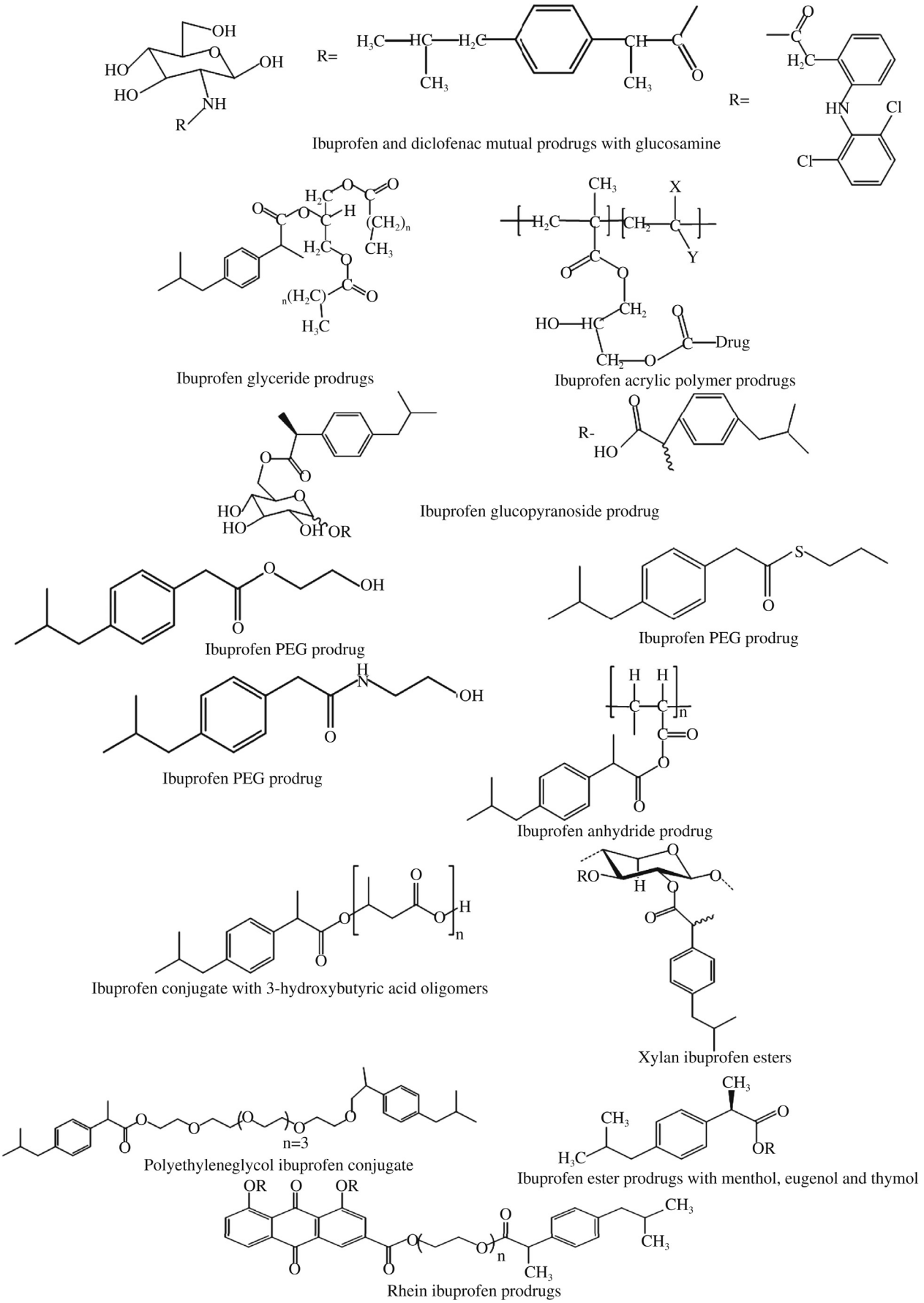
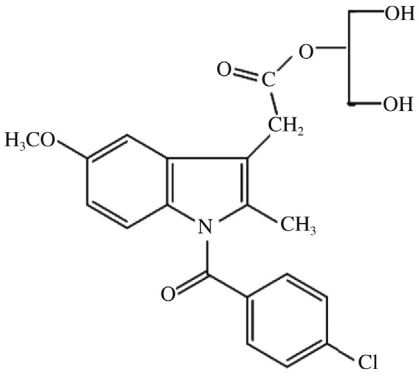
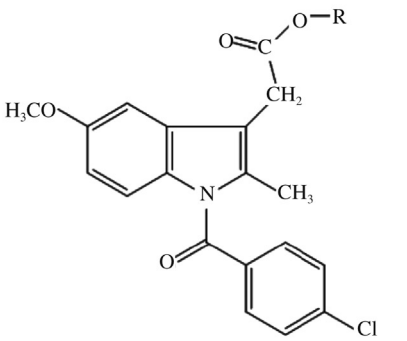


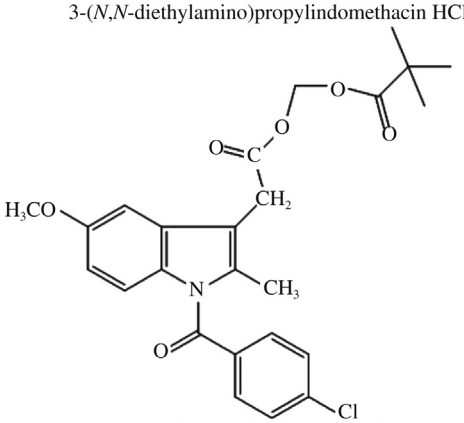
Figure 17. Prodrugs of ibuprofen.



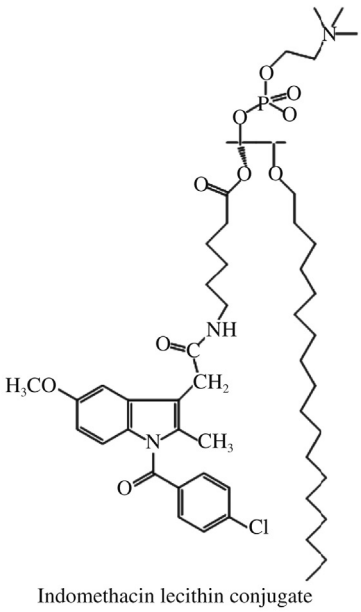
Indomethacin glyceride prodrug



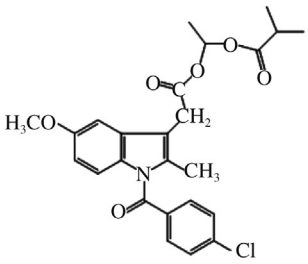
3-(*N*,*N*-diethylamino)propylindomethacin HCl



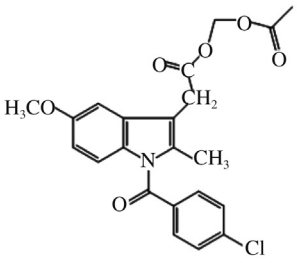
Indomethacin ester prodrug



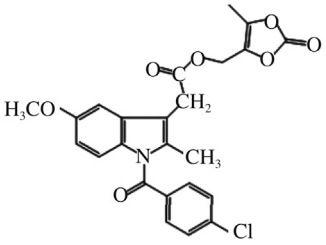
Indomethacin lecithin conjugate



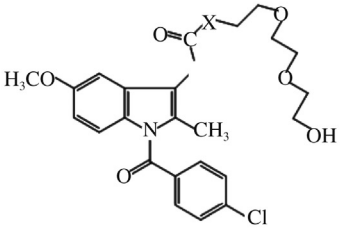
Indomethacin ester prodrug



Indomethacin ester prodrug

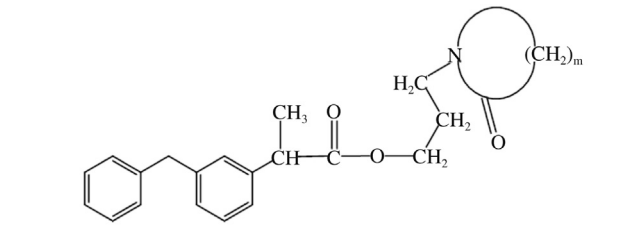


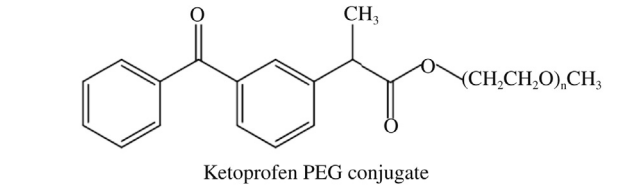
Indomethacin ester prodrug



Indomethacin tetraethylene glycol prodrug

Figure 18. Prodrugs of indomethacin.





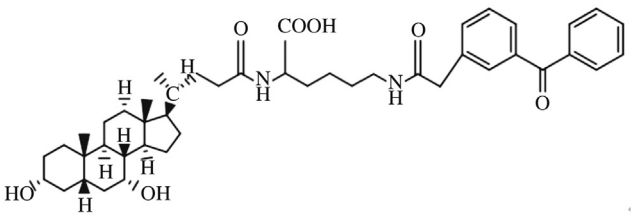


Figure 19. Prodrugs of ketoprofen.

above problem[97]. The prodrugs obtained were structurally listed in Figure 20.

1.17. Loxoprofen

Loxoprofen is a non-selective cyclooxygenase inhibitor and reduces the prostaglandin synthesis. Fluoro-loxoprofen presented in Figure 21, exhibited higher plasma concentration with limited gastric lesions[98].

1.18. Mefenamic acid

Mefenamic acid effectively inhibits the prostaglandin synthesis[99]. It has similar degree of ulcerotoxicity. In addressing this issue, with assistance of computational method, a series of ester prodrugs which were multidrug resistance-associated protein inhibitors were synthesized and they exhibited efflux mechanism[100]. Reduced ulcerogenicity was reported with mefenamic acid prodrugs which are linked with L-glycine and L-tyrosine by Schotten–Baumann method[101]. Similar effect was recorded with mefenamic acid-paracetamol mutual prodrug[102]. The fabricated prodrugs with their structure were given in Figure 22.

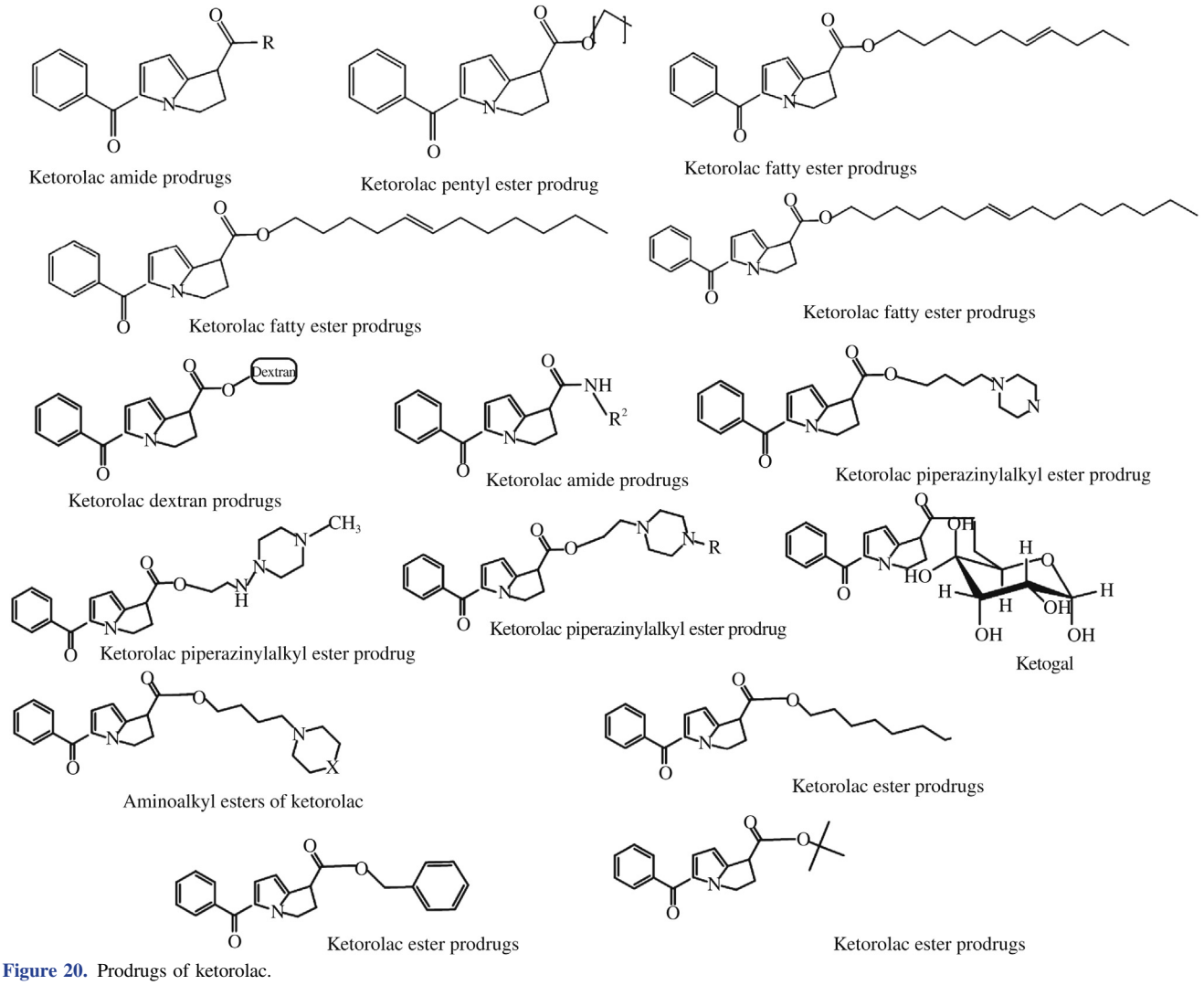
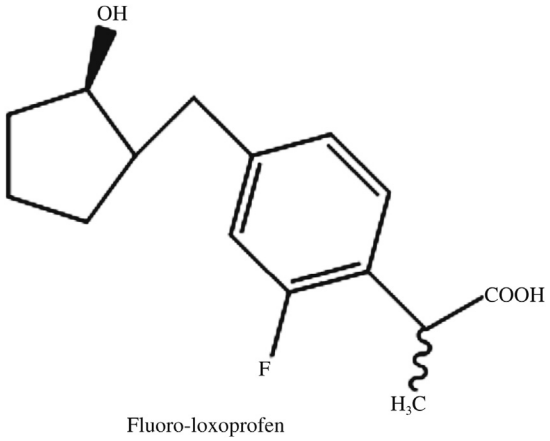


Figure 20. Prodrugs of ketorolac.



Fluoro-loxoprofen

Figure 21. Prodrugs of loxoprofen.

1.19. Naproxen

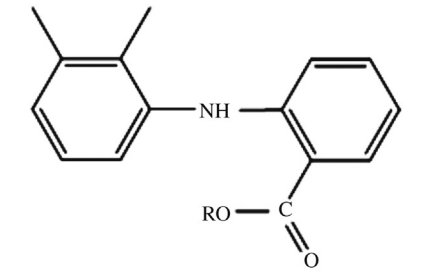
Carboxylate moiety of naproxen interacts with Arg-120 of COX-2 via hydrogen bonding[103]. Its oral use is limited due to its low absorption and high gastric toxicity. Earlier naproxen dextran prodrugs were synthesized for colon specific delivery[104]. Prodrugs as safe alternative to naproxen with reduced gastric ulceration were bagged by ester and amide prodrugs[105] and naproxen–propyphenazone mutual prodrug[106]. Later on many reports were tabled on naproxen prodrug process. In that process, series of N-substituted glycolamides[107], naproxen and ibuprofen bioconjugate prodrugs *i.e.* DL-ibuprofen amino acid conjugates, ibuprofen and naproxen stigmasterol and estronyl ester prodrugs, ibuprofen and naproxen prodrugs with protected sugars[108], naproxen glycine conjugate[109] and naproxen 1-(nitrooxy)ethyl esters[110] were outreached. On other hand, improved skin permeation was trapped by morpholinyl and piperazinyl alkyl esters of naproxen[111]. This successful process was uninterruptedly continued to synthesize prodrugs using N- and S-nitroxypivaloyl cysteine derivatives to have weak activity against COX-1[112]. Controlled release was recorded by naproxen, ketoprofen and ibuprofen using vinyl ether type polymer as conjugate[113]. *N*,*N*-dimethyl glycolamide ester prodrugs[114] and naproxen-polymer conjugates using PEG had shown their stability against acidic hydrolysis[115]. Naproxen-dendritic L-Asp and L-Glu peptide conjugates synthesized by convergent approach paved a new pathway for new bone targeting systems[116]. Brain specific delivery was achieved by glucosyl thiamine disulfide-naproxen prodrugs by coupling reaction[117] and also with prodrugs containing dihydropyridine-ascorbic acid[118]. Figure 23 describes the structures of prodrugs.

1.20. Nimesulide

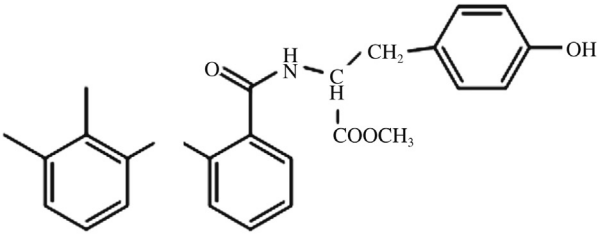
Nimesulide acts as a potent NSAID by preferentially inhibiting COX-2, release of histamine from mast cells and basophils, hydroxyl radicals, superoxide radicals and the production of hypochlorous acid by activated polymorphonuclear neutrophil leucocytes. Thus, inhibition of leukotrienes, proinflammatory cytokines, neutrophil adherence and expression of receptors resulted[119]. Due to above mechanism, nimesulide is probably less prone to GI bleeding compared to other NSAIDs. Nimesulide prodrugs as shown in Figure 24, were processed with PEG by ester and amide linkages for reduced ulcer index[120].

1.21. Others

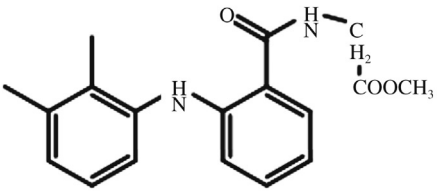
Drugs containing carboxylic acid group mostly have their decreased therapeutic effectiveness due to unfavourable physicochemical and biopharmaceutical issues. In such cases, problems were addressed by conjugating moieties like naproxen, diclofenac, valproic acid, probenecid, clofibric acid, penicillin G, dicloxacillin and ibuprofen with tertiary amido methyl ester by aminomethylation method[121]. Other mutual ester prodrugs of ibuprofen, naproxen and mefenamic acid were conjugated with



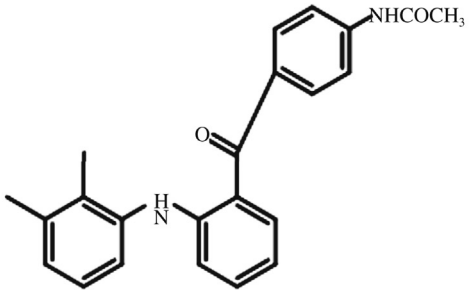
Mefenamic acid ester prodrugs



Tyrosine conjugate of mefenamic acid

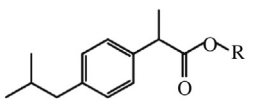


Glycine conjugate of mefenamic acid

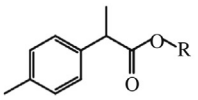


Mefenamic acid-paracetamol mutual prodrug

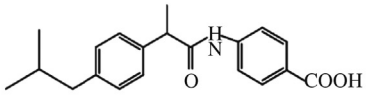
Figure 22. Prodrugs of mefenamic acid.



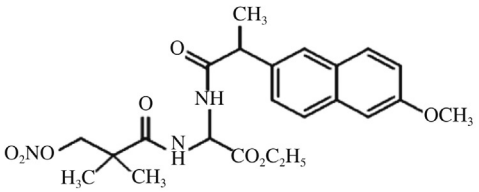
Ester prodrugs of ibuprofen



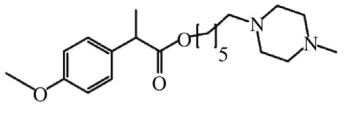
Ester prodrugs of naproxen



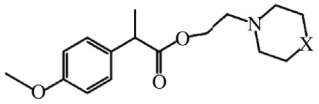
Amide prodrug of ibuprofen



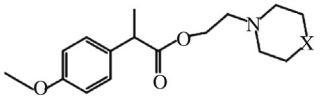
Naproxen S-nitrooxypivaloyl-cysteine derivative



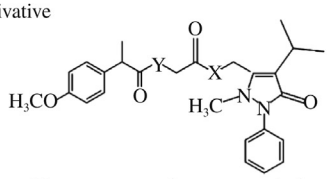
Piperazinylalkyl prodrugs of naproxen



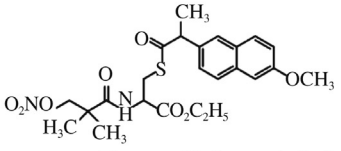
Piperazinylalkyl prodrugs of naproxen



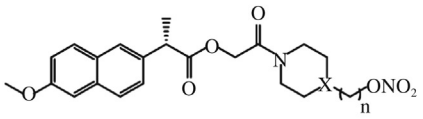
Piperazinylalkyl prodrugs of naproxen



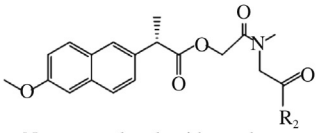
Naproxen-propyphenazone mutual prodrug



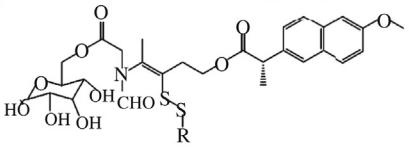
Naproxen N-nitrooxypivaloyl-cysteine derivative



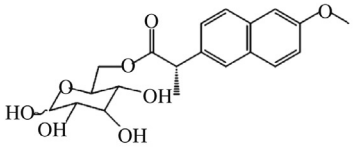
Naproxen glycolamide prodrugs



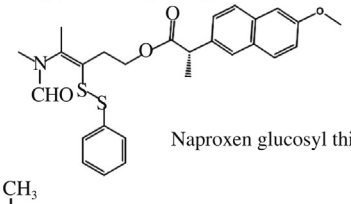
Naproxen glycolamide prodrugs



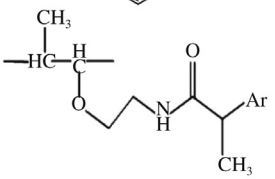
Naproxen glucosyl thiamine disulfide prodrugs



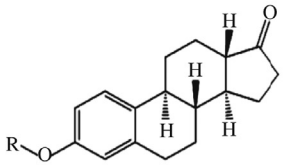
Naproxen glucosyl thiamine disulfide prodrug



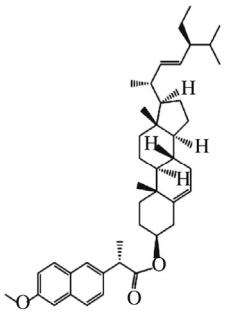
Naproxen glucosyl thiamine disulfide prodrug



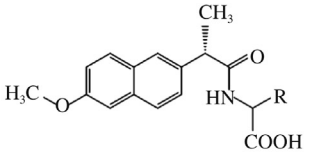
Ibuprofen, naproxen and ketoprofen vinyl ether type polymeric prodrugs



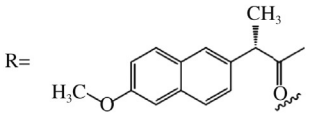
Naproxen prodrug with estrone

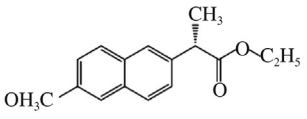


Naproxen prodrug with stigmasterol

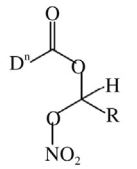


Naproxen amino acid ester prodrugs

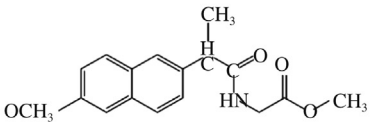




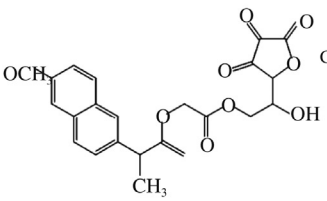
Naproxen ethyl ester



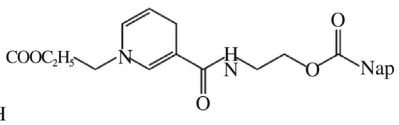
Naproxen 1-(nitrooxy)ethyl ester prodrug and aspirin



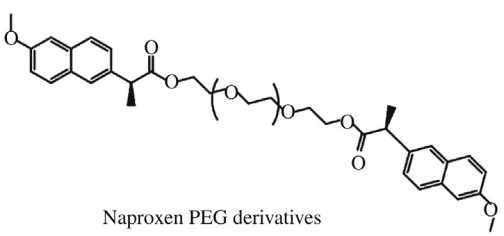
Naproxen glycine conjugate



Naproxen ascorbic acid prodrug

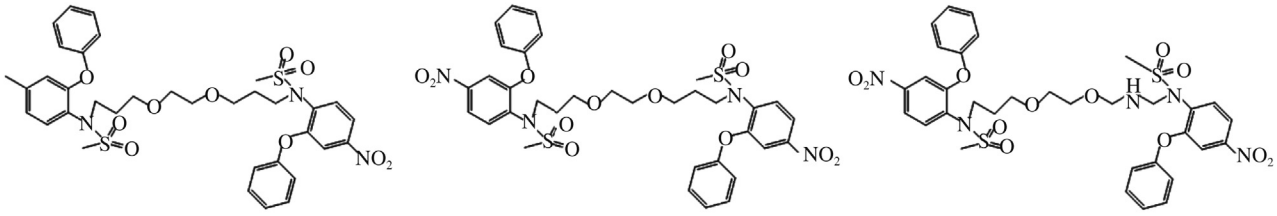


Naproxen dihydropyridine prodrug



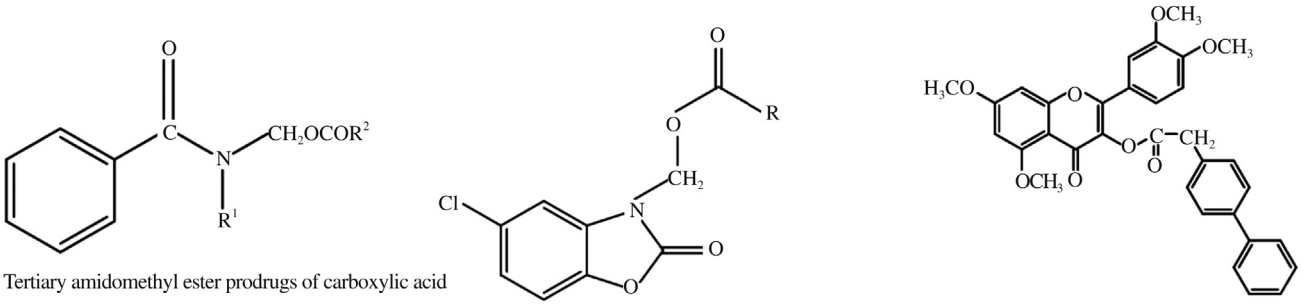
Naproxen PEG derivatives

Figure 23. Prodrugs of naproxen.



Nimesulide PEG prodrug Nimesulide PEG prodrug Nimesulide PEG prodrug

Figure 24. Prodrugs of nimesulide.



Tertiary amidomethyl ester prodrugs of carboxylic acid

Carboxylic acid mutual prodrugs

Mutual prodrug of 4-biphenylacetic acid and quercetin tetramethyl ether

Figure 25. Prodrugs of carboxylic acids.

chlorzoxazone[122], 4-biphenylacetic acid and quercetin tetra methyl ether[123] successfully. The prodrugs were structurally summarized in Figure 25.

2. Conclusion

Prodrug approach is one of the potential approaches to formulate NSAID moieties with ulcerogenicity and poor permeation. The NSAID-prodrugs, have shown a substantial improvement in the reduction of ulceration, intestinal bleeding, mucosal haemorrhage upon their oral administration. With this context, this article focused and explained clearly about NSAID-prodrugs on their history, rationale, various types, mechanisms, principles, methods employed in certain cases and therapeutic outcomes of currently used drug candidates in clinical practice with retrospective approach. The prodrug approach was successful to enhance the stability of potent NSAID moieties as well. In comparison to parent drugs, prodrug moieties are advantageous in terms of solubility and lipophilicity. Overall, acute and chronic inflammations and pains can be managed effectively with the prodrugs of NSAID category without any ulcerotoxicity and other GI complications which becomes lesser burden from the pharmacoeconomic point of view.

Conflict of interest statement

The authors report no conflict of interest.

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