Review Article

Various Ester Prodrugs of NSAIDs with Low Ulcerogenic Activity

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Received: 15-11-2018; **Revised:** 20-12-2018; **Accepted:** 02-01-2019.

ABSTRACT

The design and synthesis of different prodrugs for nonsteroidal anti-inflammatory drugs (NSAIDs) have been given much attention by medicinal chemists in last decade, esters are one of them. This review will focus on NSAID ester prodrugs that have little to non-ulcerogenic activity. Majority of the efforts were given to design prodrugs of non-selective cyclooxegenase (COX) inhibitors to masking the free acidic groups in these molecules in order to protect the gastrointestinal tract (GIT) from local irritation. Commonly, a prodrug is synthesized from a parent drug by covalently linking it, with or without a carrier, to a pharmacologically inert promoiety, which can be cleaved enzymatically and/or chemically upon administration, releasing the parent drug.

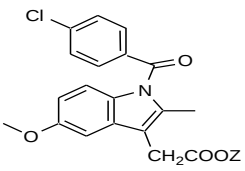
Keywords: Esters, prodrugs, NSAIDs, low ulcergenicity.

INTRODUCTION

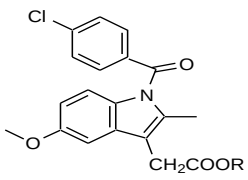
The terms prodrug was first introduced by Adrien Albert in 1958 [1]. Prodrugs are "bioreversible derivatives of drug molecules that undergo an enzymatic and/or chemical transformation *in vivo* to release the active parent drug, which can then exert the desired pharmacological effect" [2]. NSAIDs are a group of compounds that are mainly used to reduce fever, pain and inflammation. NSAIDs exert their pharmacological action by inhibiting the synthesis of prostaglandins (PGs) by non-selectively blocking cyclooxygenases 1 and 2 (COX-1 and COX-2) or by selectively blocking COX-2. Inhibition of COX-1 is partly responsible for gastrointestinal ulcerogenicity, which are the most frequent side effects of NSAIDs. Like most other drugs, prodrugs are usually taken orally, and in most cases, their stability in simulated GIT conditions is tested. Adequate chemical stability in the GIT is desired or even required for prodrugs, especially if they are NSAID prodrugs [3].

Esters Prodrugs of NSAIDS

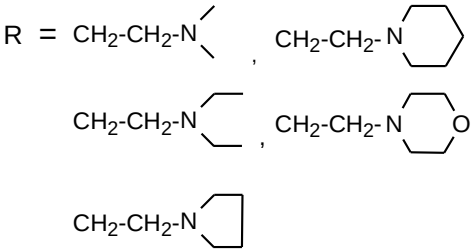
A series of ester derivatives of indomethacin (I) were synthesized and evaluated as selective COX-2 inhibitors. Conversion of indomethacin into esters and amides provided a facile strategy for generating highly selective COX-2 inhibitors and eliminating the gastrointestinal side effects of the parent compound [4, 5].



I



II

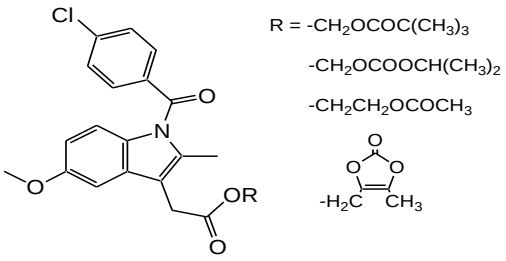


OZ = NR_1R_2 or OR

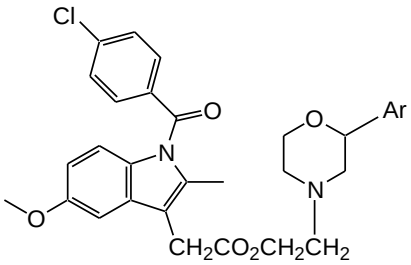
Where R = alkyl, aryl, arylalkyl

The synthesis and evaluation of five different *N,N*-disubstituted aminoethanol ester derivatives of indomethacin (II) were reported. All the esters were equipotent with indomethacin in the mouse acetic acid–induced writhing assay for analgesic action and significantly less irritating to the gastric mucosa than the parent drug [6].

Bandar *et al.* synthesized and biologically evaluated orally active esters of indomethacin (III). Few esters showed a similar degree of anti-inflammatory activity, and one was found to be less potent than the parent drug indomethacin. They were substantially less ulcerogenic than the parent drug [7].



III

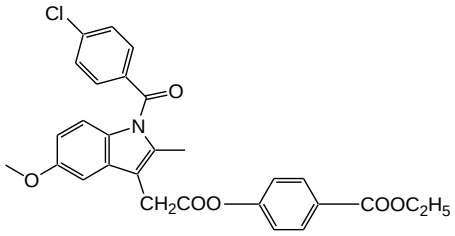


Ar = 2,4-dichloro-5-fluorophenyl

IV

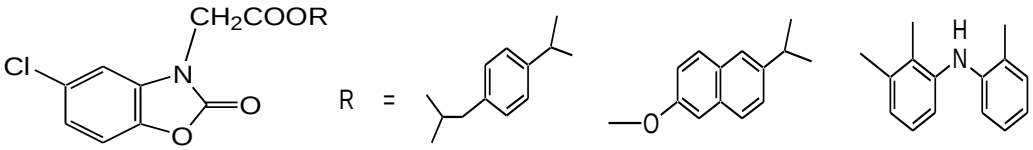
Shi *et al.* synthesized a number of novel 2-(2-arylmorpholino-4-yl)ethyl 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-acetate hydrochlorides as NSAIDs and tested for their ulcerogenic activity. Compound 2-[2-(2,4-dichloro-5-fluorophenyl)morpholino-4-yl]ethyl 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-acetate hydrochloride (IV) reduced ulcerogenic effect many times than the parent drug indomethacin [8].

Babu *et al*. prepared the ester derivatives of indomethacin. In vivo anti-inflammatory studies were carried out using carrageenan rat paw edema method and in vivo ulcerogenic studies by ulcer index method for the panel of synthesized compounds. Compound **V** displayed moderate anti-inflammatory activity with no observable ulcerogenic effect when compared to indomethacin [9].



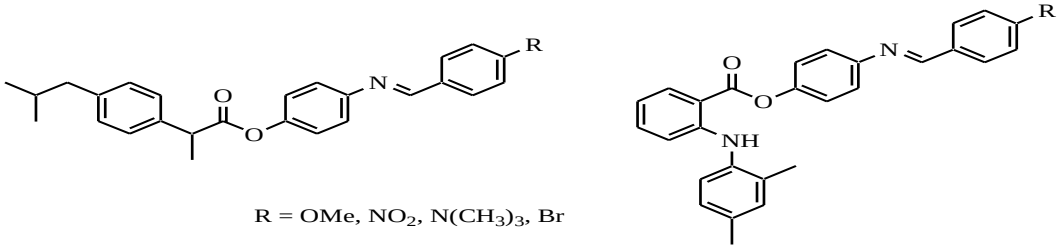
V

Ahmed *et al.* designed and synthesized new chlorzoxazone ester prodrugs (**VI)** of some acidic NSAIDs and evaluated for their anti-inflammatory activities. Scanning electromicrographs of the stomach showed that the ester prodrugs induced very little irritancy in the gastric mucosa of rats after oral administration for 4 days [10].



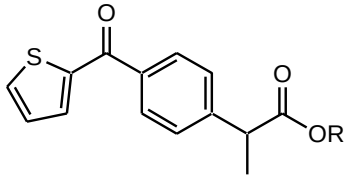
VI

Hegazy *et al.* developed a set of ibuprofenic acid and mefenamic acid esters (VII, VIII). Anti-inflammatory, analgesic as well as ulcerogenic activities of the prepared esters were evaluated in vivo and compared with that of ibuprofen as reference standard in all screenings, involving the carrageenan induced paw oedema model and hot plate method. Most of the synthesized esters showed remarkable analgesic and anti-inflammatory activities. Interestingly, all of the compounds were found to be non-ulcerogenic under the test conditions [11].



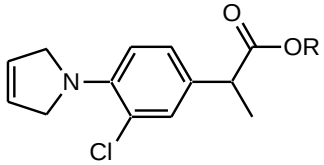
VII **VIII**

Sharma *et al*. synthesized amino acid conjugates of suprofen (IX) and pirprofen (X) by coupling the carboxylic group (as acid chloride) of the drug (suprofen or pirprofen) and various amino acid methyl ester hydrochlorides. The amino acid conjugates were evaluated for analgesic, anti-inflammatory and ulcerogenic activities. The results suggest that the amino acid conjugates showed comparable analgesic and anti-inflammatory activities to the free drug with marked reduction in ulcerogenicity [12, 13].



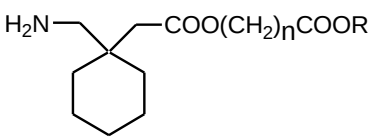
R = Amino acid

IX



R = Amino acid

X



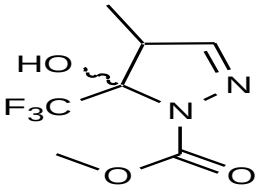
R= Mefenamic acid, n=2.

R=Naproxen, n=2. R=Ibuprofen, n=2, 3.

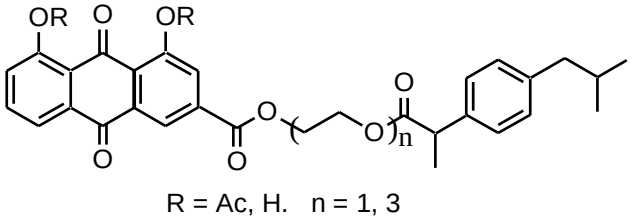
XI

Mahdi *et al*. (conjugated some NSAIDs with gabapentin via ester bonds using glycol spacers with the expectation of reducing gastric adverse effects and obtaining synergistic analgesic effects. Compounds XI showed significant stability in buffer solutions with half lives ranging from about 8–25 h, while the underwent a reasonable plasma hydrolysis (49%–88%) in 2 h. These compounds are stable during their passage through the GIT until reaching the blood circulation [14].

Milano *et al.* synthesized and evaluated the antinociceptive potential of few novel 5-trihalomethylated-4,5-dihydro-1*H*-pyrazole methyl ester compounds on chemical and thermal models of pain in mice. Compound XII was found to possess very little ulcerogenic potential. [15]



XII

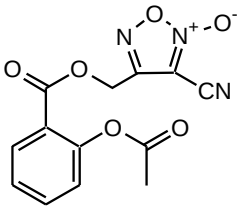


R = Ac, H. n = 1, 3

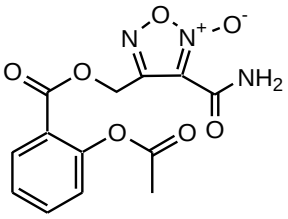
XIII

Cai *et al.* thought that rhein and NSAIDs are potent anti-inflammatory drugs but their use has been limited by the high incidence of gastrointestinal erosions. They synthesized a series of rhein–NSAIDs prodrugs (XIII) containing anthraquinone. In the target moiety rhein was linked with NSAIDs through glycol ester. Hybrid rhein–NSAIDs prodrugs exhibited significant anti-inflammatory activity, moreover, the tested compounds were also found to possess less degree of ulcerogenic potential [16].

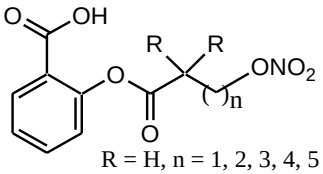
Cena *et al* synthesized new derivatives (XIV**,** XV) of NSAIDs in which aspirin is joined by an ester linkage to furoxan moieties with different ability to release NO and tested for NO-releasing, anti-inflammatory and ulcerogenic properties. The derivatives described present an anti-inflammatory trend; they are devoid of acute gastrotoxicity, principally due to their ester nature [17].



XIV



XV

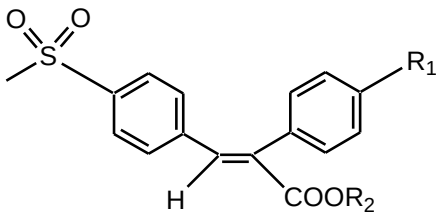


R = H, n = 1, 2, 3, 4, 5
R = CH_3, n = 1

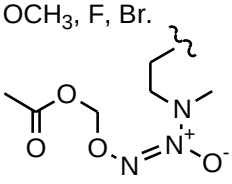
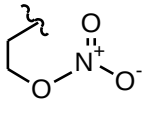
XVI

Lazaretto *et al* synthesized a new class of products (XVI) in which the phenol group of salicylic acid is linked to alkanoyl moieties bearing nitrooxy functions and studied for their polyvalent actions. The products were stable in acid and neutral media, while they were hydrolyzed in human serum. The products showed anti-inflammatory activities similar to aspirin when tested in the carrageenan-induced paw edema assay in the rat. They showed reduced or no gastrotoxicity in a lesion model in rats [18].

Abdellatif *et al*. synthesized a new group of hybrid nitric oxide-releasing anti-inflammatory ester prodrugs (XVII) wherein an O^2-acetoxymethyl-1-(*N*-ethyl-*N*-methylamino)diazen-1-ium-1,2-diolate, or 2-nitrooxyethyl, NO-donor moiety is attached directly to the carboxylic acid group of (*E*)-3-(4-methanesulfonylphenyl)-2-(phenyl)acrylic acids. Hybrid ester anti-inflammatory/NO donor prodrugs offer a potential drug design concept targeted toward the development of anti-inflammatory drugs that are devoid of adverse ulcerogenic effects [19].



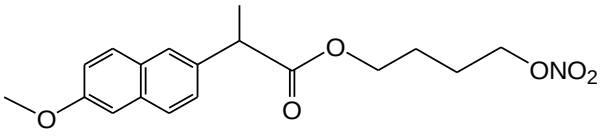
R_1 = H, OCH_3, F, Br.

R_2 =  or, 

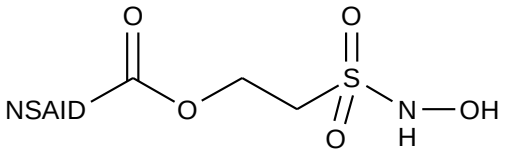
XVII

Fiorucci reported that naproxcinod (naproxen nitroxybutyl ester) (XVIII) is a nitric oxide derivative of the nonsteroidal anti-inflammatory drug naproxen and is currently in phase III clinical development for the

treatment of osteoarthritis. Preclinical studies have demonstrated that naproxcinod causes less gastric injury than naproxen, although it exerts similar anti-inflammatory and analgesic activity [20].



XVIII

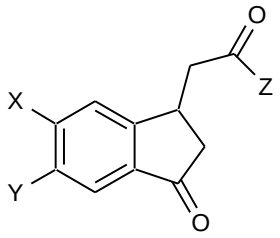


NSAID = Indomethacin, (S)-naproxen, ibuprofen

XVIX

Huang *et al*. synthesized an unknown class of ethanesulfohydroxamic acid ester prodrugs (XVIX**)** where, the carboxylic acid group of the anti-inflammatory drugs indomethacin, (S)-naproxen and ibuprofen was covalently linked via a two-carbon ethyl spacer to a sulfohydroxamic acid moiety ($CH_2CH_2SO_2NHOH$) that release NO and nitroxyl (HNO). (S)-Naproxen and ibuprofen ester prodrugs are more potent anti-inflammatory agents than their parent NSAID. Indomethacin ester prodrug, in contrast to indomethacin which is highly ulcerogenic, showed no visible stomach lesions [ulcer index (UI) = 0 for a 80 µmol/kg oral dose] while retaining potent anti-inflammatory activity, and unlike indomethacin which is an ulcerogenic selective COX-1 inhibitor, is a selective COX-2 inhibitor (COX-2 selectivity index = 184) devoid of ulcerogenicity that is attributed to its high COX-2 selectivity index and/or ability to release cytoprotective NO [21].

Different esters of (5,6-dimethoxy-3-oxo-2,3-dihydro-1*H*-inden-1-yl)acetic acid, (5-ethoxy-6-methoxy-3-oxo-2,3-dihydro-1*H*-inden-1-yl)acetic acid and (6-chloro-3-oxo-2,3-dihydro-1*H*-inden-l-yl)acetic acid (XX) were synthesized and were evaluated for their anti-inflammatory and analgesic activities, where aspirin was used as the standard . The ester derivatives of (5-ethoxy-6-methoxy-3-oxo-2,3-dihydro-1*H*-inden-1-yl)acetic acid showed highest activity among the three series, due to their higher lipophilicity. Few selected compounds were also screened for their antipyretic and ulcerogenic potential. The compounds showed no ulcer formation up to the tested dose level [22, 23].



Where,

Z = OH, OR (R = Alkyl gr.)

1. X=Y= OCH_3
2. X= OCH_3, Y= OC_2H_5
3. X = Cl, Y = H.

XX

CONCLUSION

This review is based on literature of ester prodrugs of NSAIDs that protects gastric toxicity. It will develop the idea that a lot many researchers may be involved in developing safer NSAIDs. This literature would help the scientist to get the preliminary idea of the research done in the field of prodrugs as NSAIDs. This will help to generate the view that development of NSAIDs as prodrug is required due to the side effects they have. This paper would lead to generate the idea how the safer NSAIDs can be developed which may be fruitful for the society.

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Source of Support: Nil, **Conflict of Interest:** None.