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VARIOUS PRODRUGS OF NSAIDS WITH LOW TOXICITY – A REVIEW

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ABSTRACT

The design and synthesis of mutual prodrugs for nonsteroidal anti-inflammatory drugs (NSAIDs) have been given much attention by medicinal chemists. NSAIDs are the most widely used prescribed and over the counter (OTC) medications. This review article focuses on the mutual prodrugs of NSAIDs with reduced GIT toxicity. Many researchers have synthesized the Prodrugs of NSAIDs and evaluated for their biological activities. The present review provides an in-depth view of work done so far on prodrugs of NSAIDs and its biological activities covering analgesic, anti-inflammatory, and ulcerogenic activities. Majority of the efforts were given by medicinal chemist to design ester, amide and mutual prodrugs of for masking the free carboxylic groups to protect the gastrointestinal tract (GIT) The free acidic group is responsible for the GIT toxicity because it generates the oxygen reactive species. Commonly, a prodrug is synthesized from a parent drug by covalently linking it, with or without a spacer, to a pharmacologically active promoiety or ester and amide prodrugs of NSAIDs, which can be cleaved enzymatically and/or chemically upon administration, releasing the parent drug.

Keywords: NSAIDs, Prodrugs, analgesic, anti-inflammatory, ulcerogenicity, OTC

INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are medicines that are used for management of pain, inflammation and a high temperature. They are often used to relieve symptoms of headaches, painful periods, sprains and strains, colds and flu, arthritis, and other causes of long-term pain. Many of the Over-the-counter (OTC) NSAIDs and Prescription NSAIDs available in the market. The chemical structure of some commercially available OTC and Prescription NSAIDs are Shown in **Figure 1[1].**

Secreation of Prostaglandins via COX pathway, which are major physiological and pathological mediators in inflammation, pain, pyrexia, cancer and neurological diseases. By blocking the COX enzyme results in the reduction of synthesis of prostaglandins, which leads to decrease in inflammation, pain and fever. The reduction of prostaglandins secreation 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 inhibit not only COX-2 but also COX-1 which cause GI ulceration and potentially upper GI perforation and bleeding because the GI mucosal injury produced by NSAIDs **[2]**.

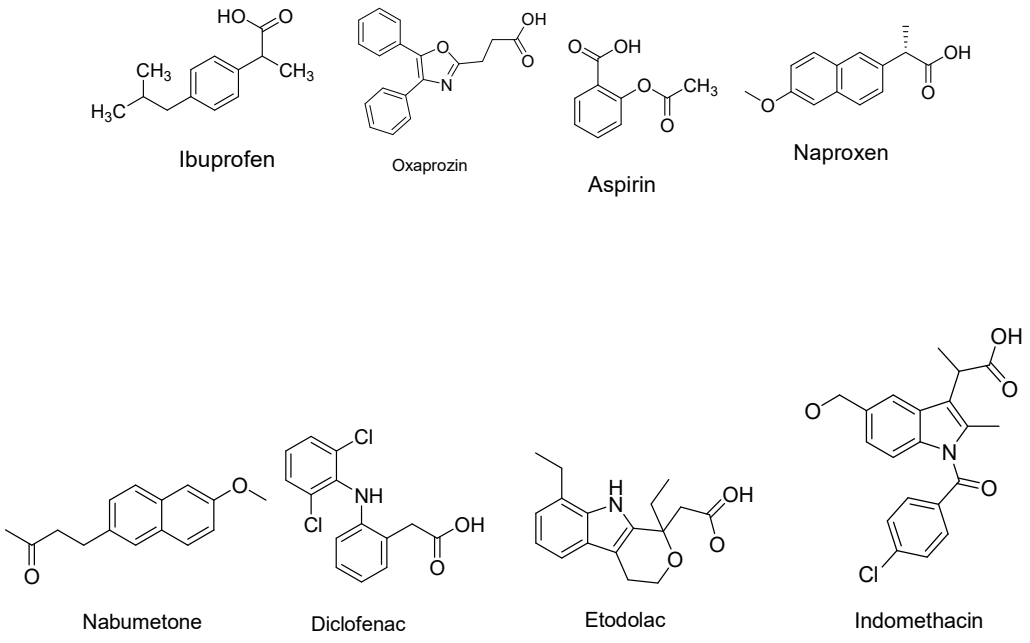

Figure 1: The chemical Structure of some commercially available NSAID Prodrugs

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NSAIDs show undesirable physicochemical properties as explained above and their therapeutic efficacy can be improved by prodrug approach. NSAIDs were converted to various ester or amide prodrugs which reduce the toxicity produce by NSAIDs. One of the effective methods of modern research in the field of medicine is the development of prodrugs that have gained increasingly more importance in current therapy. A prodrug refers to a pharmacologically inactive compound which is transformed into an active substance by either chemical or metabolic processes. In some cases, a prodrug may consist of two pharmacologically active drugs that are coupled with each other in a single molecule, so that each drug acts as a promoiety for the other, which is called "Mutual prodrugs". Many of the approved prodrugs available in the market shown in **Figure 2 [4]**.

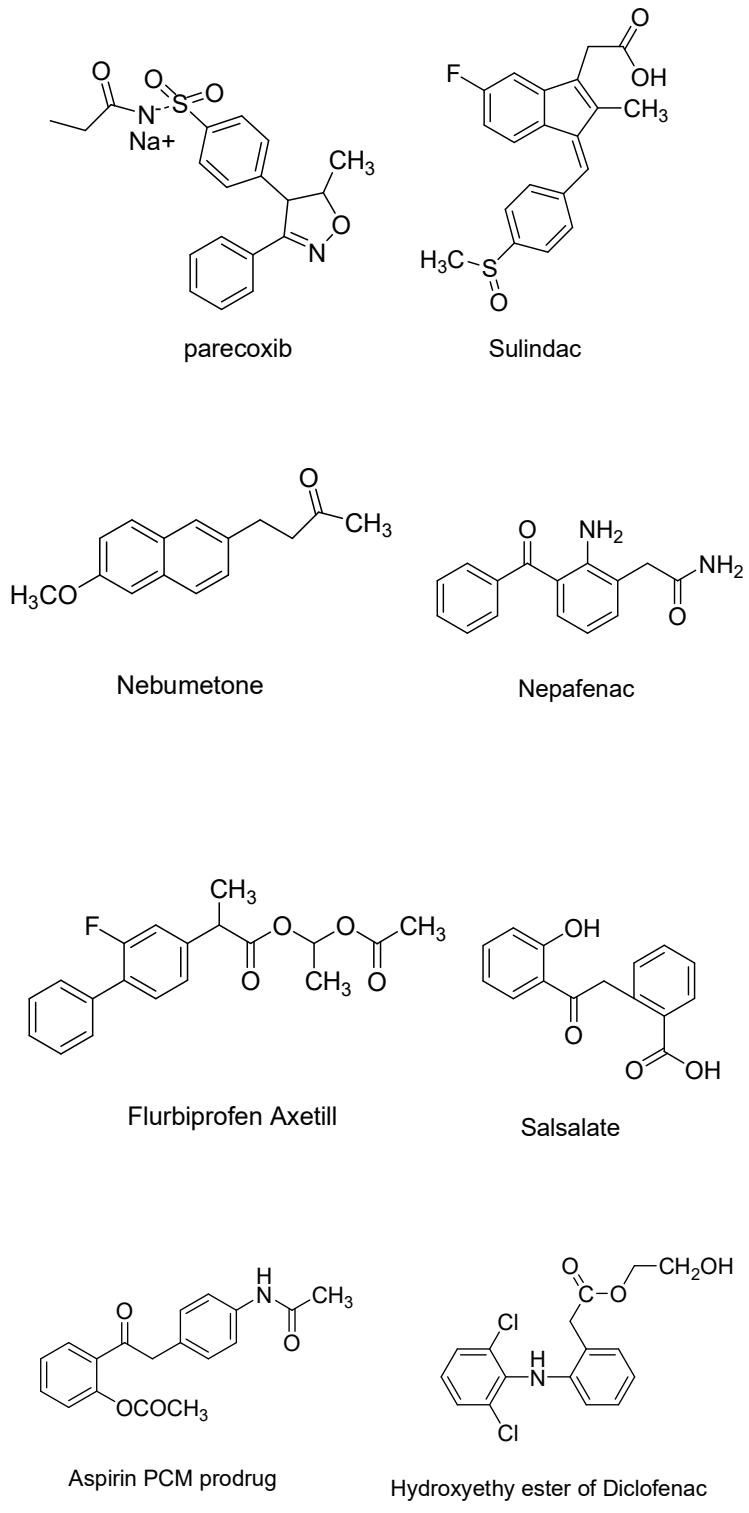


Figure 2: The chemical Structure of some commercially available NSAID Prodrugs

DISCOVERY AND DEVELOPMENT OF PRODRUGS:

Sucheta *et al*. **[6]** synthesize mutual prodrugs of Ibuprofen with Propyphenazone by direct coupling and by using spacer technique (amino acid was taken as a spacer) which reduce the gastrointestinal (GI) toxicity. The structures of synthesized prodrugs were confirmed by spectral methods. The mutual prodrugs were evaluated for their drug release behavior in enzyme-free simulated gastric fluid (SGF, pH 1.2) and simulated intestinal fluid (SIF, pH 7.4). Both IBU prodrugs shows better analgesic activity along with much-reduced ulcerogenic than parent drug. Prodrug IP1 showed better analgesic activity and negligible ulcerogenic tendency than IP2, and hence it could be considered as a better candidate for prodrug among the two.

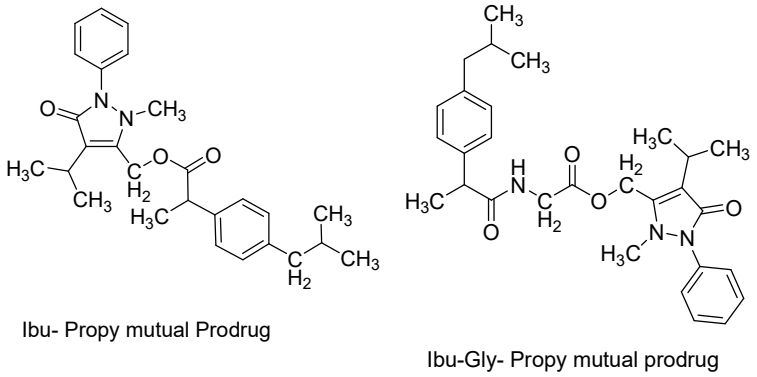


Figure 3: The chemical structure of IBU-propyphenazone ester (IP1)

Atul R. Bendale *et al*. **[7]** synthesizedamino acid (tryptophan, glycine, histidine) aceclofenac prodrugs which improves the solubility and to overcome the general side effects of NSAID. Though the amino acid conjugates comes under prodrug but it overcome the limitation of prodrug such as formation of unexpected metabolite and undesirable side effects. Amongstthese Tryptophan-Aceclofenac conjugate had maximum water solubility, while in methanol and chloroform solubility of remaining synthesized compounds shows greater result than parent compound. Present research work indicates that conjugates synthesized with hydrophilic amino acid possess more water solubility.

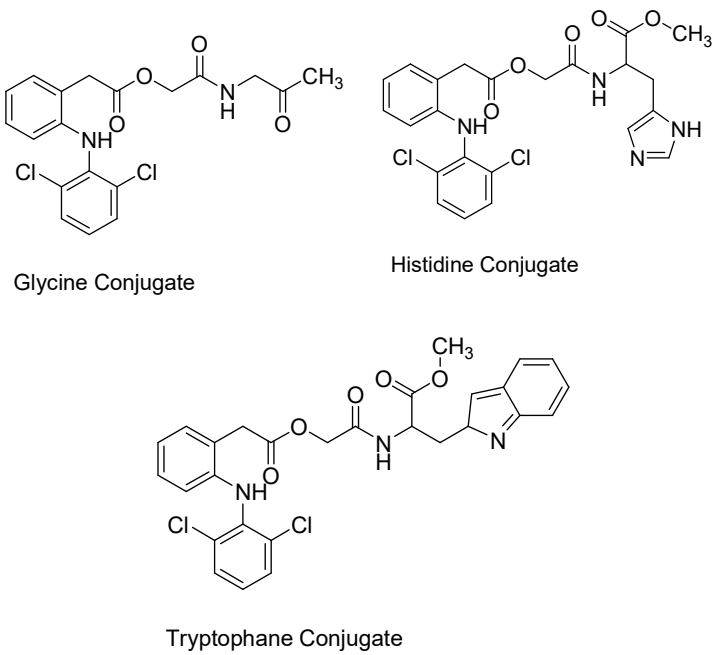
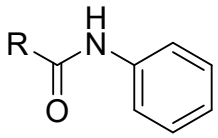


Figure 4: The chemical Structure of Aceclofenac Prodrugs

Asif Husain *et al*. **[8]** synthesize prodrugs of commonly used NSAIDs to overcome the gastrointestinal toxicity (irritation and bleeding) associated with their use. A total of six amide-based prodrugs (Ia-f) of aceclofenac, diclofenac, fenbufen, indomethacin, mefenamic acid and 4-biphenyl acetic acid were synthesized through one-pot method (single step synthesis). All the synthesized prodrug gives better anti-inflammatory activity then parent drugs. Prodrugs of diclofenac and mefenamic acid shows slightly less activity than the parent drug. The highest increase in antiinflammatory activity was observed in the case of prodrug of 4-biphenyl acetic acid which showed 76.14% inhibition whereas its parent drug, 4-biphenyl acetic acid, showed 72.08% inhibition.



R1- Aceclofenac
R2- Diclofenac
R3- Fenbufen
R4- Mfenamic acid
R5- Indomethacin

Figure 5: The chemical Structure of Amide based Prodrugs of NSAIDs

Mohamed F. *et al*. **[9]** synthesized mutual prodrugs of the widely used NSAIDs (ibuprofen, diclofenac, and ketoprofen) with propyphenazone. The three prodrugs exhibit in vivo anti-inflammatory and analgesic activities with improved therapeutics potency over each parent drug. Additionally, prodrugs shows COXIactivity (COXII IC50 of 0.97 ± 0.04 μM, compared to no observed inhibition of COXI at 160 μM). Inhibition of COXII suppresses inflammatory diseases without affecting COXI-mediated GI tract events.

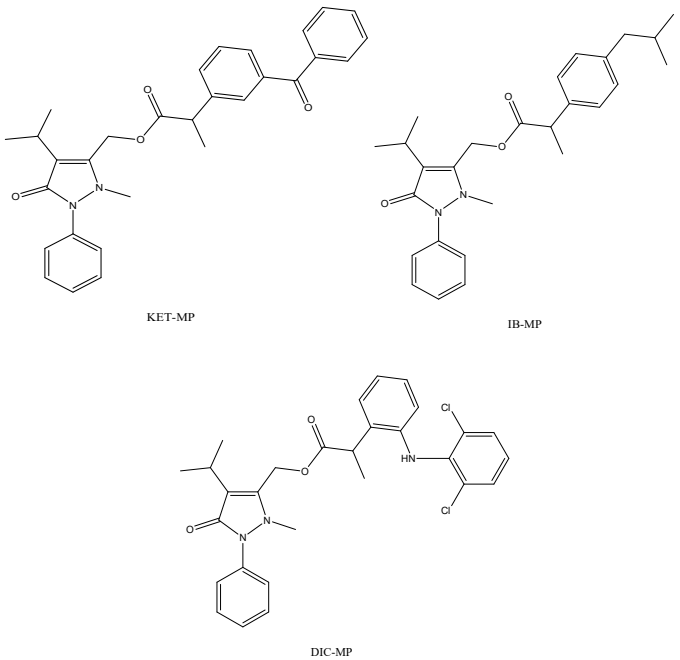
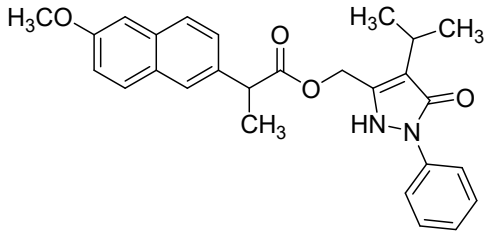
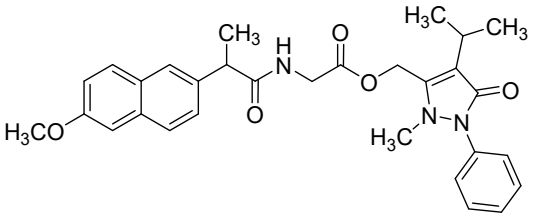


Figure 6: The chemical Structure of Prodrugs of propyphenazone with NSAIDs

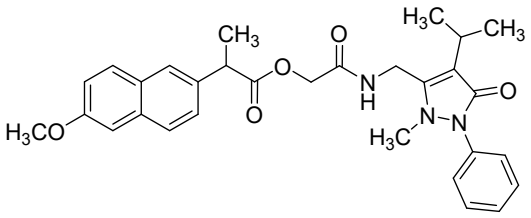
Mahmoud Sheha *et al* **[10]** synthesized Naproxen–propyphenazone (NAP-PP) esters as prodrugs with the aim of improving the therapeutic index through prevention of gastrointestinal irritation and bleeding. The structures of the synthesized NAP-PP hybrid esters were confirmed by spectral data. In vitro hydrolysis studywas performin two different non-enzymatic buffer solutions, at pH 1.2, and 7.4 as well as in liver homogenates. Study of analgesic and anti-inflammatory properties in comparison with the reference compounds has shown that both analgesic and anti-inflammatory activities were present at the same doses of the investigated compounds. The prodrugswere found to be less irritating to gastric mucosal membrane than the parent drugs. These results shows that the synthesized prodrugs are characterized by better therapeutic index than the parent drugs.



NAP- HMP Prodrug



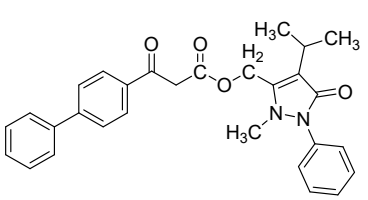
NAP-Gly- HMP Prodrug



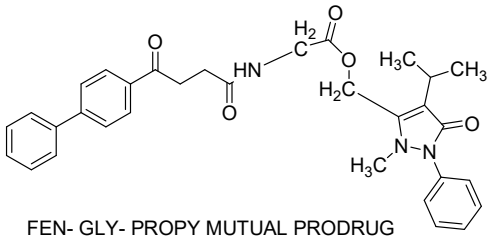
NAP-Ac- HMP Prodrug

Figure 7: The chemical Structure of Naproxane Prodrugs

Himanshu *et al* **[11]** synthesized Mutual prodrugs of fenbufen and propyphenazone with the aim of getting better therapeutic index through avoidance of gastrointestinal problems and to check the efficiency of release of parent drug in the presence of spacer. These mutual prodrugs were synthesized by direct esterification and by using glycine as a spacer. From the results obtained it was concluded that these compounds exhibit better biological activity and less gastro-intestinal side effects than parent drug fenbufen.



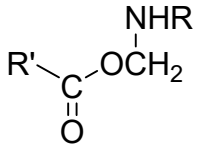
FEN- PROPY MUTUAL PRODRUG



FEN- GLY- PROPY MUTUAL PRODRUG

Figure 8: The chemical Structure of fenbufen Prodrugs

Monther F Mahdi *et al*. synthesized mutual prodrugs of NSAIDs with different sulfa drugs using glycolic acid spacer (-OCH2COO-) to reduce the ulcerogenic side effects of NSAIDs, by masking free carboxyl group of the NSAIDs that responsible for the local irritation. Two NSAIDs, ibuprofen and naproxen each one of them were linked to two different sulfa drugs sulfathiazole and sulfadiazine through glycolic acid spacer (-OCH2COO-) as possible mutual prodrugs to reduce the ulcerogenic side effects of NSAIDs by esterfication of the free carboxyl group of the NSAIDs that responsible for the local irritation.



Compound 1a R=Sulphathiazole

Compound 1b R' =Sulphathiazole

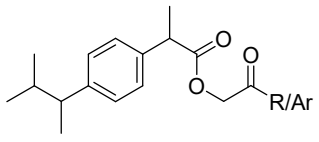
compound I :1a and R= Ibuprofen
compound II: 1b and R' = Ibuprofen

compound III: 1a and R' = Naproxane

compound IV: 1b and R' = Naproxane

Figure 9: The chemical Structure of Prodrugs of NSAIDs with sulpha drugs

Datta M. Avhad *et al*. synthesized mutual prodrug of Ibuprofen. The local generation of various „reactive oxygen species" play a significant role in the formation of gastric ulceration associated with NSAIDs therapy. This indicates antioxidants may prevent gastric ulceration due to NSAIDs. Mutual prodrugs of Ibuprofen were planned for treatment of inflammation along with antioxidants property.



Ibuprofen- Menthol/Vaniline Prodrug

Figure 10: The chemical Structure of amide Prodrugs of Ibuprofen

Zaman Ashraf *et al* were synthesized Flurbiprofen–antioxidant mutual prodrugs to reduce the gastrointestinal (GI) effects associated with flurbiprofen. For reducing the GI toxicity, the free carboxylic group (–COOH) was temporarily masked by esterification with phenolic –OH of natural antioxidants vanillin, thymol, umbelliferone, and sesamol. Molecular docking and simulation study ware carried out with cox proteins and it is observed that prodrug had more potential to selectively bind to COX-2 than COX 1.

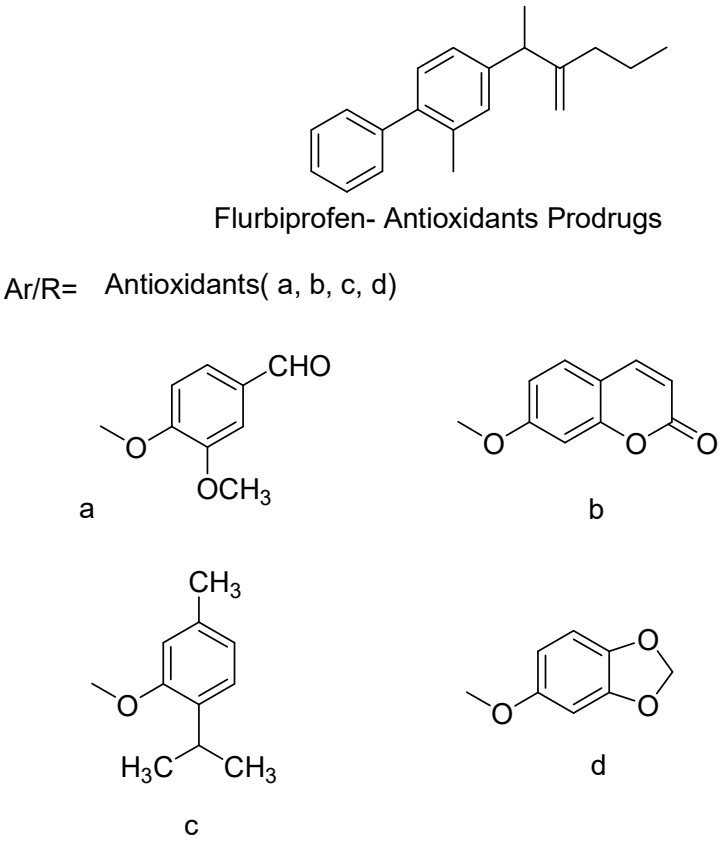
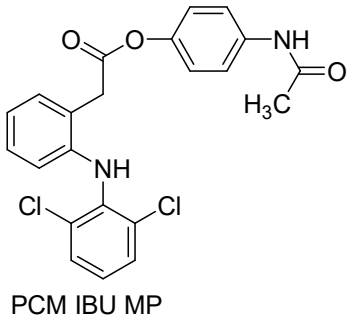


Figure 11: The chemical Structure of Flurbiprofen antioxidants Prodrugs

Perumal *et al*. synthesized mutual prodrug of diclofenac sodium and paracetamol. In vitro hydrolysis of prodrug in HCl buffer (pH 1.2) and phosphate buffer (pH 7.4) showed that the drug was released more in pH 7.4. The purity of the compound was confirmed by TLC and characterized on the basis of IR spectroscopy and 1 H NMR spectroscopy. The physiochemical parameters were determined and the results showed that they are more lipophilic than the parent drug. The compound was also evaluated for anti-inflammatory and ulcerogenicity.



PCM IBU MP

Figure 12: The chemical Structure of PCM-IBU Prodrugs

Ashutosh Mishra *et al*. synthesized Ten prodrugs of FB by amidation with ethyl esters of amino acids, namely, glycine, L-phenylalanine, L-tryptophan, L-valine, L-isoleucine, L-alanine, L-leucine, L-glutamic acid, L-aspartic acid and B alanine. The structure of Synthesized prodrugs was confirmed by spectral data.In vivo evaluation of Synthesized prodrugs were performed forbioavailibility studies, analgesic, anti-inflammatory activities and ulcerogenic index. Marked reduction of ulcerogenic index and comparable analgesic, anti-inflammatory activities were obtained in all cases as compared to FB. Among synthesized prodrugs 3 compounds showing excellent pharmacological response and encouraging hydrolysis rate both in (Simulated Intestinal Fluid) SIF and in 80% human plasma. Such prodrugs can be considered for sustained release purpose.

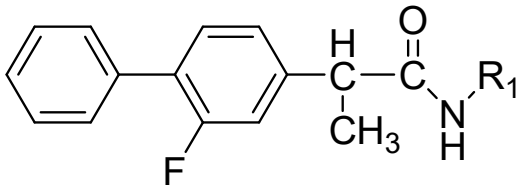


Figure 13: The chemical Structure of amide Prodrugs of flurbiprofen

CONCLUSION:

NSAID drugs are the commonly used over the counter and prescribed medication. Most of the NSAIDs having carboxylic acid group which is responsible for various Side effects of these drugs.In general, the reduction in these side effects is achieved by masking of the carboxylic acid group. 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 review article focused on the 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. In this review article we discuss about the various mutual prodrugs of NSAIDs.Many researchers have synthesized ester, amide and mutual prodrugs of various prodrugs of NSAIDs by direct coupling or by using spacer techniques. In comparison to parent drugs, prodrug moieties are more advantageous in terms of solubility and lipophilicity. Overall, inflammation and pains can be managed effectively with the prodrugs approach without any ulcerotoxicity and other GI complications which becomes lesser burden from the pharmacoeconomic point of view.

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