

MEFENAMIC ACID PRODRUGS AND CODRUGS - TWO DECADES OF DEVELOPMENT

Alaa Abu-Jaish¹, Gennaro Mecca², Salma Jumaa¹, Ameen Thawabteh¹,
Rafik Karaman*^{1,3}

¹Pharmaceutical Sciences Department, Faculty of Pharmacy, Al-Quds University, Jerusalem, Palestine.

²Exo Research Organization, Potenza, Italy.

³Department of Science, University of Basilicata, Potenza, Italy.

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***Correspondence for
Author**

Dr. Rafik Karaman
Pharmaceutical Sciences
Department, Faculty of
Pharmacy, Al-Quds
University, Jerusalem,
Palestine.

ABSTRACT

prodrugs are bioreversible derivatives of drug molecules that undergo intermolecular or intramolecular reactions by enzymatic or chemical biotransformation in the human body to give the corresponding active parent drugs and a non-toxic promoiety. Prodrugs have been extensively and successfully used as a chemical tool for modification of the physicochemical, pharmacokinetic as well as pharmacodynamic characteristics of commonly used drugs and new drugs. This mini review focuses on the design, synthesis and pharmacological effects of several prodrugs and codrugs of the non-steroidal anti-inflammatory (NSAIDs), mefenamic acid. Exploitation of the prodrug approach has the potential to achieve a reduction of mefenamic acid GI (gastro-intestinal) intolerance, enhance its bioavailability, mask its unpleasant

sensation and prolong its duration of action. In addition, utilizing the prodrug concept might enhance the bioavailability of the counter partner drug of mefenamic acid codrug by increasing its lipophilicity.

KEYWORDS: Anti-inflammatory drugs, Mefenamic acid prodrugs, Mefenamic acid codrugs, Prodrugs chemical approach, NSAIDs drugs, Prodrugs catalyzed by enzymes.

INTRODUCTION

Prodrugs are molecules which are lacking any pharmacodynamic properties and therefore are not biologically active by themselves, however, they exert a therapeutic effect when they are inter- or intraconverted to their active parent drugs by chemical or enzymatic processes.^[1]

Prodrug design is an essential part of the drug discovery and development. Prodrugs can offer a variety of advantages over their parent active forms; such advantages include an increased in solubility, enhanced stability, improved bioavailability, reduced side effects, masked unpleasant taste and odor and better selectivity.^[2] Therefore, utilizing the prodrug approach might improve the physicochemical properties of a drug and hence increase its bioavailability and therapeutic efficiency.^[1, 3]

The first time the prodrug concept used was in the middle of the twentieth century by Parke-Davis Company during a study conducted on a modification of chloramphenicol structure for improving its unpleasant taste and poor solubility in water. As a result of this study twochloramphenicol prodrugs were synthesized: chloramphenicol sodium succinate having goodwater solubility for use in IV, IM and ophthalmic administration, and chloramphenicolpalmitate to be administered in the form of suspension for pediatrics and geriatrics.^[4, 5]

The conventional and accepted method for prodrugs classification is based on the drug's derivatization and linker's type. Using this method prodrugs are divided into two sub major classes: (i) carrier-linked prodrugs, in this class the linker is covalently attached to the active drug, however, drug-linker linkage has to be accessible to undergo cleavage via enzymatic or chemical processes to yield the active parent drug and a nontoxic and non-immunogenic linker which must be ready for removal by *in vivo* elimination.^[6, 7] This class is usually subdivided into three sub-classes: (1) bipartite which consists of one linker (promoiety) attached directly to the active parent drug, (2) tripartite which involves a spacer or connecting moiety between the drug and linker. Generally, known bipartite prodrugs are stable, however, in some examples they may suffer instability due to the nature of the drug linker linkage and (3) mutual prodrugs, which involve two drugs linked together.

(ii) Bioprecursors which are molecules lacking any therapeutic effect however, upon *in vivo* metabolism they furnish new entities that may be active or further may be metabolized to active metabolites. Examples for such class might involve an amine which is metabolized to aldehyde and the latter into carboxylic acid. In this class of prodrugs there is no linker

(carrier) but the bioprecursors should be readily metabolized to induce the appropriate functional groups.^[1, 4, 8]

During the past two decades extensive research has been done to promote and accelerate the use of prodrugs to replace a number of marketed drugs having low bioavailability as a result of one or more pharmacokinetic barriers. The prodrug approach has been successfully and significantly applied to a wide range of drugs. Statistics have shown that currently more than 10% of the world-wide drugs available in the pharmaceuticals market can be classified as prodrugs. In addition, it is estimated that about 20% of drugs having small molecular weights approved during the period 2000-2008 were prodrugs, and in the year 2008 alone, more than 33% of approved drugs were prodrugs.^[9]

Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most widely over the counter (OTC) and prescribed drugs used throughout the world. Historically, the NSAIDs had their origin in the serendipitous discovery of some plants where the extracts of those plants had been applied for pain relief, fever and inflammation conditions.^[10, 11]

NSAIDs exert their therapeutic effects by inhibiting the synthesis of prostaglandins (PGs) by non-selectively blocking cyclooxygenases 1 and 2 (COX-1 and COX-2). COX-1 is constitutively expressed in stomach to provide cytoprotection in the GIT. COX-2 is inducible and plays a major role in prostaglandin biosynthesis in inflammatory cells.^[11]

In the past few years, epidemiological studies have indicated that NSAIDs are neuroprotective^[12] therefore, their prolonged use reduces the risk of Alzheimer's.^[13] In addition, recent clinical studies have provided evidence that NSAIDs are promising anticancer agents as well.^[14, 15]

Pain sensation can be associated with different disease statements. Women in the world suffer from extensive pain during their menstrual cycle which is accompanied with heavy bleeding. NSAIDs have been shown to reduce blood loss by 20-49% and can be used for an indefinite number of menstrual cycles.^[16]

Therefore, the relationship between oral intake of NSAIDs and gastrointestinal (GI) sideeffects, in some cases life threatening conditions, limits the NSAIDs clinical usefulness. Non-steroidal anti-inflammatory drugs with tranexamic acid are the first line therapy to treat pain associated with bleeding. It has been shown to be effective in reducing heavy menstrual

bleeding and pain especially in women using intrauterine devices (IUDs). There are potential advantages in giving such co-administered drugs having complementary pharmacological activities in the form of a single chemical entity in order to increase patient compliance. Abnormal uterine bleeding and pain are the most common medical reasons for premature discontinuation of the intrauterine device (IUD). The IUD is the most common method of reversible contraception worldwide (147 million current users), so premature discontinuation affects large numbers of women. Each year, an estimated 40 million women have an IUD inserted. From 5% to 15% of women discontinue IUD use within one year because of bleeding or pain.^[16]

On other hand, mefenamic acid and diclofenac have unpleasant bitter taste associated with numbness of the tongue, which limits their use as an oral dosage form especially in pediatric and geriatric patients.^[17] Conventional taste masking methods such as the use of sweeteners, amino acids and flavoring agents alone are often inadequate in masking the taste of highly bitter drugs. Another approach is to improve the unpleasant taste by masking the functional group in the drug that is responsible for its bitterness.^[18]

NSAIDs can be classified based on their chemical structure or mechanism of action:

- Salicylates.
- Propionic acid derivatives.
- Acetic acid derivatives.
- Selective COX-2 inhibitors.

The most prominent members of the NSAIDs are mefenamic acid, **1** (Figure 1), diclofenac potassium or sodium, **2**(Figure 1), ibuprofen, **3**(Figure 1), ketoprofen, **4**(Figure 1), naproxen, (Figure 1) aspirin, **6**(Figure 1), celecoxib, **7**(Figure 2), etoricoxib, **8** Figure 2). parecoxib, **9** (Figure 2), and others.

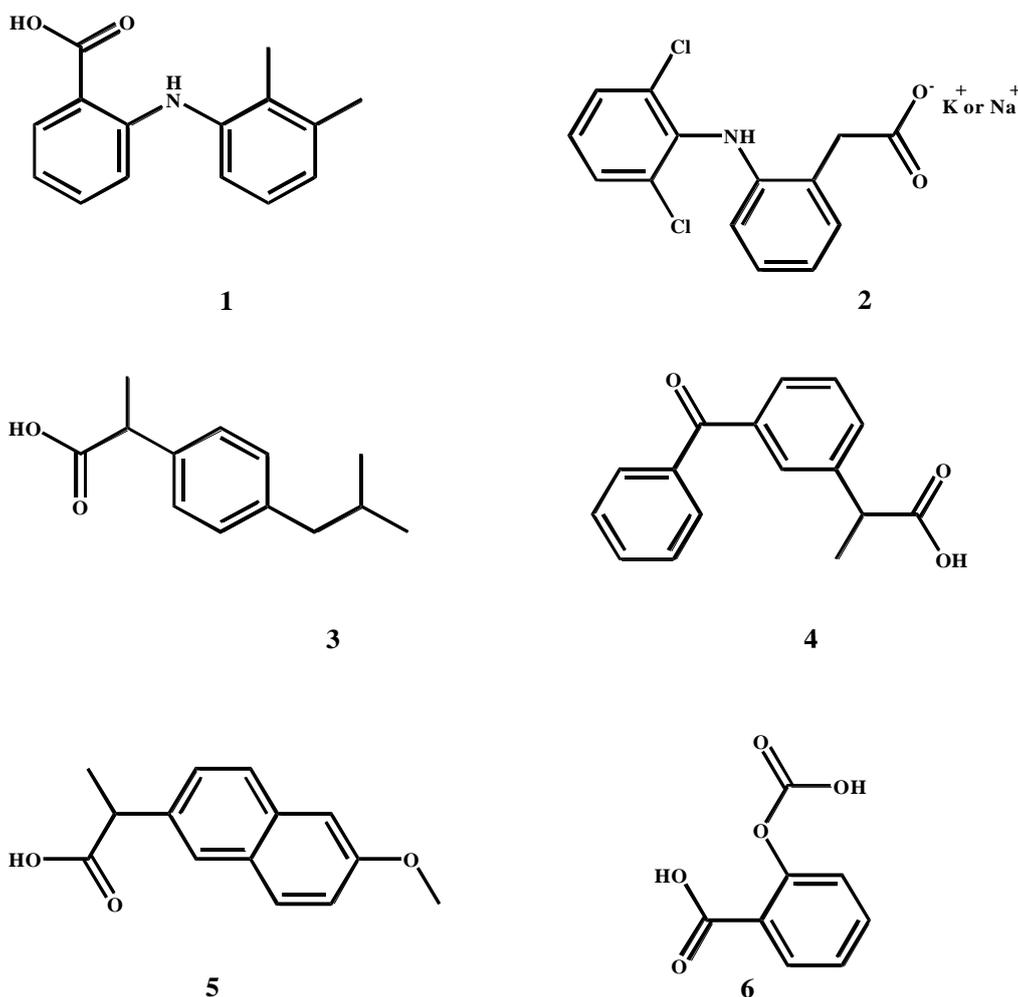


Figure 1: Chemical structures of NSAIDs 1-6

Upper gastro intestinal tract (GIT) injury constitutes the most frequent of all adverse reactions of NSAIDs and often these reactions lead to GIT ulceration and hemorrhage. Gastro intestinal (GI) mucosal injury produced by NSAIDs is generally believed to be caused by two different mechanisms: a local action exerted by direct contact of a drug with gastric mucosa caused by the free carboxyl acid group and a generalized systemic action following absorption which is believed to be caused by inhibition of the COX 1, a constitutive form of COX.^[19] Intolerance of GI side effects leads to withdrawal rates of about 10% of NSAIDs users. Furthermore, nonselective NSAID users are four to eight times more likely to develop gastro duodenal ulcers during therapy.^[20]

Not widely appreciated, NSAIDs use results in death as well. Few studies have estimated mortality resulting from GI complications of NSAIDs. Among the available reports, estimates attributable to NSAIDs have widely varied from 3,200 to higher than 16,500 deaths per year in the United States (Figure 3).^[21]

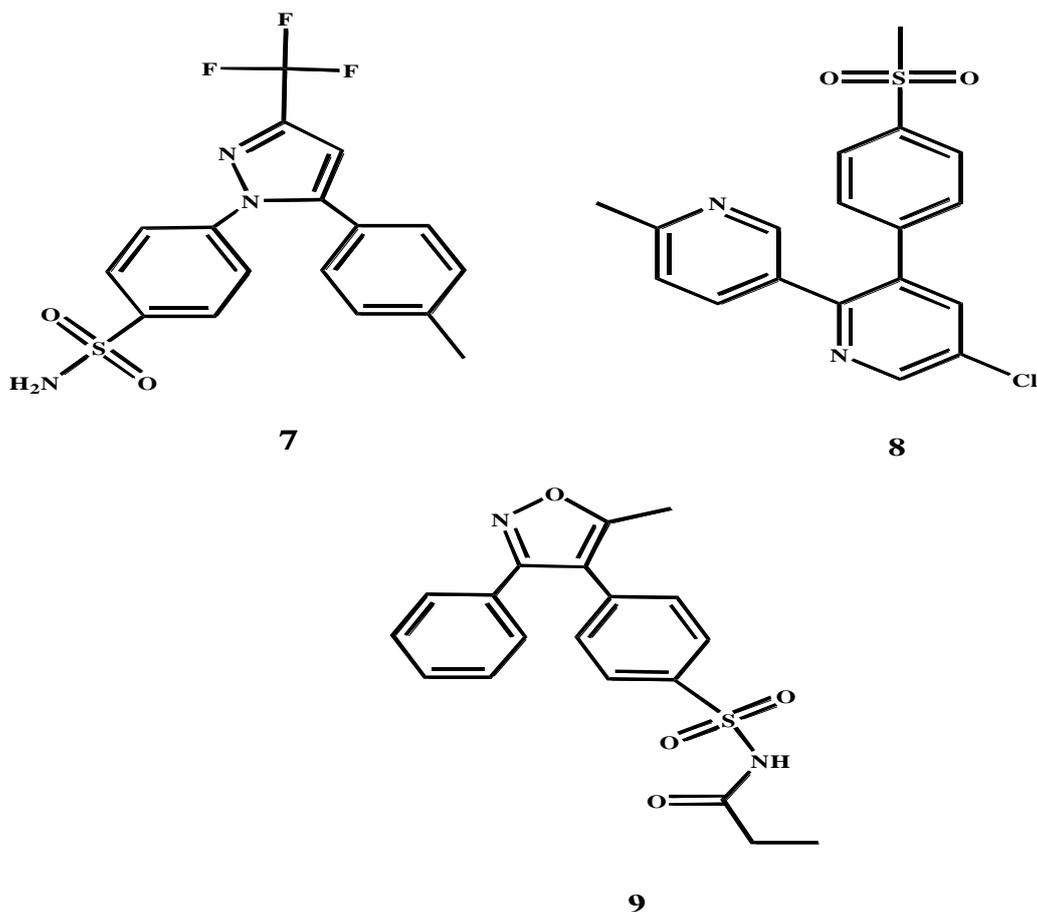


Figure 2: Chemical structures of NSAIDs 7-9.

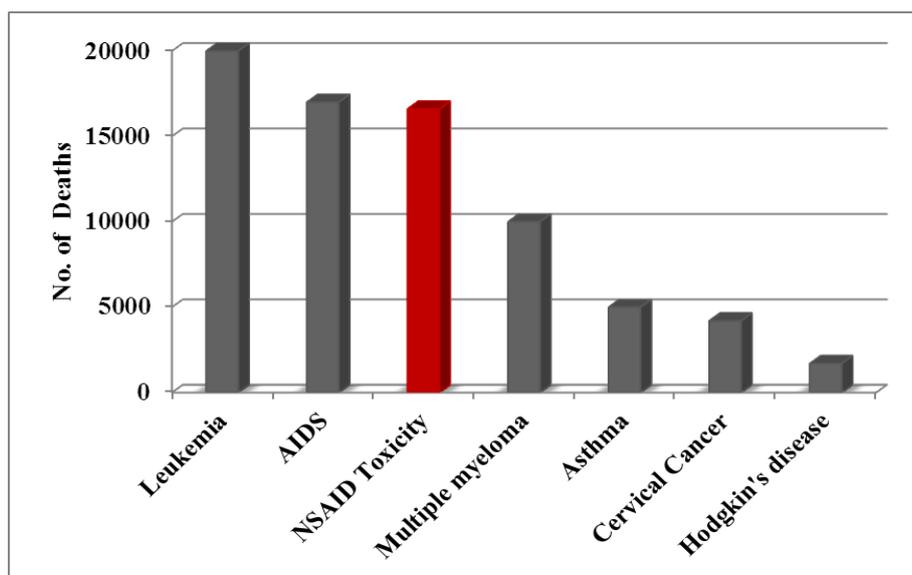


Figure 3: Mortality statistics for different drugs and diseases in the United States 1997.^[21]

The world market for NSAIDs is approximately \$8 billion. The cost of treating NSAID-related gastrointestinal adverse effects almost certainly exceeds this amount. The

annual cost of treating NSAID gastropathy in rheumatoid arthritis patients in the USA, for example, have been reported to exceed \$4 billion.^[22]

In general, different chemical modifications have been made for obtaining NSAIDs prodrugs to overcome the side effects associated with the use of NSAIDs such as the GI side effects. These methods include:

(1) Ester and amide prodrugs; NSAIDs ester prodrugs are made via a reaction of the carboxylic group of the NSAID drug (via acyl halide) and an alcohol such as ethanol, isopropyl alcohol and etc.. Similarly, amide prodrugs have also been synthesized from the reaction of the carboxylic group of the NSAID (via acyl halide) with an amine. The amide prodrugs are relatively more stable prodrugs in the stomach than their corresponding esters as amidases which catalyze the hydrolysis of amides are present only in the intestine, (2) anhydride prodrugs of NSAIDs; since the hydrolysis of ester and amide prodrugs is dependent on the activity of esterases and amidases, respectively, and this catalysis is varied upon the time and target of the drug's administration (variable bioavailability), anhydride prodrugs of carboxylic acid drugs may solve this problem. Dissimilar to ester linkage, the anhydride linkage is more labile to hydrolysis and undergoes cleavage to its corresponding carboxylic acid in a controlled and predictable manner and it has shown less sensitivity to cleavage catalyzed by enzymes than its corresponding esters and amides,^[23] (3) mutual prodrugs of NSAIDs: they normally comprise of two biologically active agents coupled together so that each of both drugs acts as a promoiety for the other and vice versa, (4) the NSAID coupling with amino acids and (5) glucosamine conjugate prodrug of NSAIDs.

Mefenamic acid (MA) (**1** in Figure 3), is a compound belonging to the family of Naryl anthranilic acid. It is one among the most widely used NSAIDs having both antiinflammatory and analgesic activities. It has short half-life of 2 hours and 90% bioavailability. The main side effect of using mefenamic acid is an increased risk of serious gastrointestinal adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be in some cases fatal.

During the past seventeen years attempts have been made to overcome the gastrointestinal side effects associated with the use of mefenamic acid. In 1997 Jilani *et al.* have synthesized several hydroxyethyl esters of diclofenac and mefenamic acid and studied their stability in 1N HCl, buffer pH 7.4 and human plasma. Their study revealed that mefenamic acid

prodrugs were much more stable than their corresponding diclofenac prodrugs. The $t_{1/2}$ values for mefenamic acid prodrugs were 38 hours in buffer pH 10 and 7.8 hours in plasma and that of diclofenac prodrugs were 22 hours and 1.12 hours, respectively. Based on this result they concluded that mefenamic ester prodrugs are not suitable for use as prodrugs due to their high stability in plasma.^[24]

In 2002, Tantishaiyakul *et al.* have synthesized a mefenamic-guaiacol ester prodrug by reacting mefenamic acid, guaiacol, N, N'-dimethylaminopyridine, and N, N'-dicyclohexylcarbodiimide. The physicochemical properties, stability and transport across Caco-2 monolayers for the synthesized prodrug were researched. The prodrug has shown to be completely stable in aqueous buffer solutions of pH 1-10. However, it underwent hydrolysis in the presence of porcine liver esterase and Caco-2 homogenate. The transported amount of the ester was 14.63% after 3 hours with a lag time of 23 minutes. The Papp for the ester was 4.72×10^{-6} cm s⁻¹. This value suggests that the prodrug absorption was moderate.^[25]

In 2005, Almasirad *et al.* have made a number of mefenamic acid prodrugs by which the non-steroidal anti-inflammatory drug is attached to N-Arylhydrazone derivative. The aim of their study was to obtain new compounds having analgesic and anti-inflammatory activity without GI side effects. The synthesized prodrugs were tested for analgesic and anti-inflammatory activities by abdominal constriction (writhing test) and carrageenan-induced rat paw edema tests, respectively. Their study results revealed that most of the synthesized prodrugs induced significant reduction in the writhing response compared to the control samples.^[26]

In 2005, Khan *et al.* reacted mefenamic acid with 1, 2, 3-trihydroxy propane 1, 3-dipalmitate/stearate to provide new mefenamic acid ester prodrugs. The aim of their study was to make novel mefenamic acid prodrugs lacking the gastrointestinal side effect associated with their parent drug, mefenamic acid. The synthesized prodrugs were tested for gastric toxicity, anti-inflammatory activity by the carrageenan induced paw oedema test and analgesic activity by the acetic acid induced writhing method. The cleavage rate of the ester prodrugs to their parent active drug was studied at pH 3, 4, 5 and 7.4 and monitored by HPLC method. The kinetic results revealed very low hydrolysis rate at pH 5 when compared to pH 7.4. This result indicates that the drug release from the prodrugs in the pH of stomach was negligible; however, the release of mefenamic acid at pH 7.4 was in adequate amounts.^[27]

In 2007, Dev *et al.* have synthesized mefenamic acid- β -cyclodextrin prodrug. The primary hydroxy group of β -cyclodextrins was used to block the free acid group of mefenamic acid. The synthesis consisted of several protection and deprotection steps.

The study results demonstrated that the mefenamic acid- β -cyclodextrin prodrug has retained its pharmacological activity as was evident by the percentage inhibition of oedema and in acetic acid induced writhing method and comparison with the activity of its active parent drug. In addition, the study showed that the maximum activity of the ester prodrug was obtained after 6 hours indicating that there is no drug absorption in the stomach. Further, *in vitro* studies showed the ester to be completely stable in simulated gastric and intestinal fluid whereas it underwent complete hydrolysis in rat faecal contents representing the colon.

Ulcerogenicity studies showed that the ester prodrug is not ulcerogenic indicating that masking the carboxyl group in mefenamic acid is a good approach to reduce the ulcerogenicity, a major side effect of the active parent drug, mefenamic acid.^[28]

In 2009, Rasheed *et al.* have synthesized mefenamic amide prodrugs by an amidation reaction of methyl esters of amino acids such as histidine and tryptophan with mefenamic acid. The goal of their study was to mask the free hydroxyl group of mefenamic acid which is responsible for the adverse effects of gastrointestinal origin associated with the use of the NSAID drug. The hydrolysis rates, antiinflammatory and analgesic activities as well as ulcer index of the synthesized amide prodrugs were investigated. The results indicated marked reduction of ulcer index and comparable anti-inflammatory activity of the prodrugs as compared to mefenamic acid. In addition, the amide prodrugs showed excellent pharmacological response and encouraging hydrolysis rate both in SIF and SIF+ 80% human plasma. Based on this result the authors concluded that both amide prodrugs are more efficient than their active parent drug and are advantageous due to the fact that they possess lesser gastrointestinal side effects than mefenamic acid.^[29]

In 2010, Rasheed *et al.* have synthesized two mefenamic acid-amide prodrugs, mefenamic acid-tyrosine and mefenamic acid-glycine via multi-step synthesis which involved protection and deprotection reactions. Pharmacological activity test and kinetic studies on both prodrugs were carried out. The two prodrugs kinetic studies were accomplished in simulated gastric fluid, simulated intestinal fluid, and 80% plasma. In addition, the analgesic, anti-inflammatory, and ulcerogenic activities for both prodrugs were evaluated. Mefenamic acid-

glycine prodrug showed analgesic activity of 86%, and both mefenamic acid-tyrosine and mefenamic acid-glycine prodrugs showed more efficient anti-inflammatory activity (74% and 81%, respectively) than that of their parent drug, mefenamic acid (40%). Moreover, the study indicated that the average ulcer index of the two newly synthesized prodrugs was lower (9.1 and 4.5) than that of mefenamic acid (24.2). Based on the study results the authors concluded that both prodrugs are more efficient than mefenamic acid and are advantageous since their gastrointestinal side effects are lesser than of their parent drug, mefenamic acid.^[30]

In 2011, Uludag *et al.* have synthesized ibuprofen, ketoprofen, and mefenamic acid ester and amide prodrugs and they investigated their pharmacological activities and stability in physiological media. Their findings revealed that the synthesized prodrugs were completely stable in simulated gastric (SGF, pH 1.2) and intestinal fluids (SIF, pH 6.8).

Furthermore, they found that these prodrugs were more lipophilic than their parent active drugs, thus resulting in higher absorption than their parent drugs. Based on the lack of the hydrolysis of these prodrugs by esterases and amidases they concluded that these NSAID derivatives have potent analgesic and anti-inflammatory activity themselves and lack any gastrointestinal side effects (non-ulcerogenic). These results were supported by docking experiments of the synthesized prodrugs with the active sites of esterases and amidases which revealed a strong binding between the prodrugs and enzymes^[31]

In 2011, Velingkar *et al.* synthesized a number of mefenamic acid codrugs with and without spacer. The synthesized codrugs were tested for anti-inflammatory activity by carrageenan induced rat paw edema method; for analgesic activity by Eddy's hot plate and tail-flick method; and for ulcerogenicity and acute oral toxicity. The tests results for the codrugs revealed efficient analgesic and anti-inflammatory activity and a lack of ulcerogenicity. Hydrolysis studies demonstrated that the codrugs were stable at pH 1.2, indicating a lack of cleavage of the codrugs in the stomach. However, in human plasma (pH 7.4) the codrugs released 80% of the parent drug upon hydrolysis, whereas much lower percentage of the drug was released in aqueous buffer of 7.4, suggesting that the rate of hydrolysis in human plasma was markedly accelerated when compared to that in aqueous buffers.^[32]

In 2012, Mahdi *et al.* have synthesized a number of NSAIDs-gabapentin codrugs by which the two active parent drugs were connected by glycol spacers with the aim to reduce the gastrointestinal adverse effects associated with the use of NSAIDs. The hydrolysis of the

ester bond connecting the two drugs via glycol in two different non enzymatic buffers at pH 1.2 and 7.4, as well as in 80% human plasma was monitored by HPLC. The codrugs connected via ethylene glycol spacers showed complete stability at buffer solutions with half-lives ranging from about 8–25 hours, whereas they underwent 49%–88% hydrolysis (within 2 hours) in 80% human plasma. The kinetic study results of some of the codrugs indicate that these compounds may be stable during their passage through the GIT until reaching the blood circulation.^[33]

In 2013, Shah *et al.* synthesized a novel codrug consisting of paracetamol and mefenamic acid with the aim to reduce the ulcererogenic adverse effects associated with the use of NSAIDs. The codrug was completely characterized by standard methods, its stability at different pH values was investigated and its pharmacological properties were evaluated.

The kinetic study of the codrug was followed by HPLC at pH 2, pH 7.4 as well as in human plasma. The kinetics results showed the codrug to be stable at pH 2 and pH 7.4, however, it underwent cleavage to the parent drugs in human plasma with hydrolysis rate of $1.8908 \times 10^4 \text{ s}^{-1}$ and half-life ($t_{1/2}$) of 61.07 minutes, indicating rapid hydrolysis in plasma to release the two parent drugs. The pharmacological activities (anti-inflammatory, analgesic and ulcerogenic) were evaluated for the codrug. The ulcerogenic reduction in terms of gastric wall mucosa, hexosamine and total proteins were also determined in glandular stomach of rats. The results revealed that the codrug has an ulcer index lower than the parent drug, indicating low ulcerogenic side effects.^[34]

In 2014, Dhokchawle *et al.* have synthesized a number of mefenamic acid prodrugs by which the free carboxyl group in mefenamic acid was connected via a covalent bond with natural compounds, eugenol and vanillin. The synthesized ester prodrugs were fully characterized by standard methods and by solubility studies, partition coefficient and hydrolytic studies. The synthesized prodrugs were tested for their anti-inflammatory analgesic and ulcerogenic activity. The tests results revealed that the synthesized prodrugs have shown retention of the anti-inflammatory activity with a reduced ulcerogenicity when compared to their active parent drug, mefenamic acid.^[35]

In 2014, Kemisetti *et al.* have synthesized mefenamic acid prodrugs by which the NSAID drug was covalently attached to either polyethylene glycol 1500 or polyethylene glycol 6000 via a glycine spacer. The synthesized prodrugs were fully characterized and their hydrolysis

at buffers of pH 1.2 and 7.4 was investigated. In addition, their anti-inflammatory activity using Carrageenan induced rat paw edema method and ulcerogenicity using Pylorus ligation method were tested. The study results demonstrated that the hydrolysis rates of the prodrugs at pH 7.4 were higher than that at pH 1.2 and the anti-inflammatory activity of the prodrugs was comparable to that of their active parent drug, mefenamic acid.

Based on these results the authors concluded that the synthesized prodrugs possess anti-inflammatory activity as well as good ulcer protecting activity and can be used as a better replacement to their parent NSAID drug.^[36]

The prodrug chemical approach involving enzyme catalysis has many disadvantages related to many intrinsic and extrinsic factors that can affect the process. For instance, the activity of many prodrug-activating enzymes may be varied due to genetic polymorphisms, age-related physiological changes, or drug interactions, leading to variation in clinical effects. Therefore, there is a need to develop prodrugs that have the potential to undergo intraconversion to their parent drugs via intramolecular reaction and without a need of enzyme catalysis.^[37-39]

Recently we have been engaging in unraveling the mechanisms of a number of enzyme models for allowing the design of efficient chemical devices to be utilized as prodrug linkers that can be covalently attached to commonly used drugs which can chemically, and not enzymatically, be converted to release the active drugs in a controlled manner.^[40-75]

For example, investigating the mechanism for a proton transfer in Kirby's N-alkylmaleamic acids (enzyme model) has assisted in the design and synthesis of several prodrugs such as the anti-bleeding agent, tranexamic acid,^[76] the anti-viral acyclovir,^[77] the anti-hypertensive agent, atenolol.^[78-79] In addition, prodrugs for masking the bitter sensation of the pain killer and the antibacterial drugs, cefuroxime, amoxicillin and cephalexin were also designed and made,^[80] The linker's role in atenolol, paracetamol and the antibacterial prodrugs is to block the free hydroxyl or amine groups, which are responsible for the drug bitterness, and to enable the release of the drug in a programmable manner. Menger's Kemp acid enzyme model was utilized for the design of prodrugs of the anti-Parkinson's disease, dopamine.^[81] Prodrug of dimethyl fumarate for the treatment psoriasis was also made and studied.^[82] Furthermore, unraveling the mechanism of Kirby's acetals has led to the design and synthesis of novel prodrugs of the anti-myelodysplastic aza-nucleosides,^[83] anti-malarial atovaquone,

[84-86] anti-cholesterol agents, statins. [87] and the anti-congestant, phenylephrine. [88] In these prodrugs, the enzyme model (linker) was covalently attached to the hydroxyl group of the active parent drug such that the drug-linker moiety (prodrug) has the potential to cleave upon exposure to physiological environments such as stomach, intestine, and/or blood circulation, with rates that are only dependent on the structural features of the pharmacologically inactive linker (Kirby's enzyme model). [89-90]

Continuing our study on how to utilize enzyme models as potential carriers for drugs containing amine group, we have utilized the proton transfer reaction in the acid-catalyzed hydrolysis of N-alkyl maleamic acids (Kirby's enzyme model) [55] to design and synthesize prodrugs and codrugs of mefenamic and tranexamic acids.

The main goal of our research was to provide drugs and codrugs of mefenamic acid lacking any gastrointestinal toxicity side effects while retaining the anti-inflammatory and analgesic activity of the active parent drug. In addition, the proposed mefenamic acid prodrugs and codrugs should have the potential to undergo a chemical and not enzymatic driven cleavage, and release the active parent drug, mefenamic acid, in a controlled manner.

For fulfilling this goal two mefenamic acid amide prodrug and codrug were synthesized by reacting the acyl chloride of mefenamic acid with either tranexamic acid (Figure 4) or N,Ndimethyl amine (Figure 5). The hydrolysis reactions of the new synthesized codrug **10** and mefenamic acid amide prodrug **11** at a wide pH range were monitored by HPLC and the results obtained are listed in Tables 1 and 2

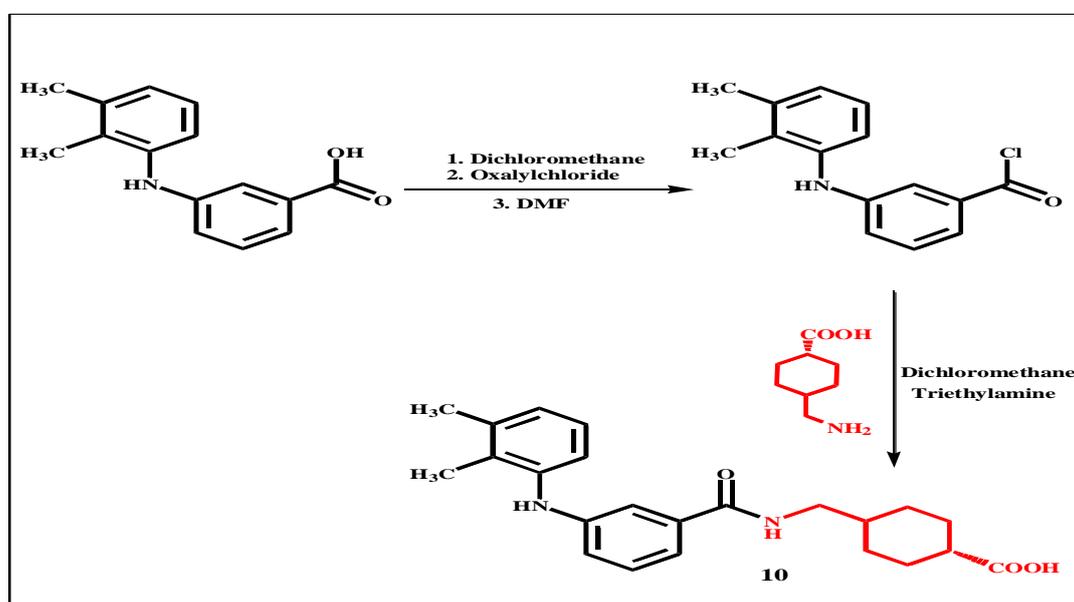


Figure 4: Synthesis pathway for mefenamic-tranexamic acids codrug, **10**.

Table 1: Hydrolysis of codrug 10 at different pHs

Medium	K_{obs} (h^{-1})	$t_{1/2}$ (h)
1N HCl	7.25×10^{-4}	1.07
Buffer pH 2.5	No reaction	No reaction
Buffer pH 5.5	No reaction	No reaction
Buffer pH 7.4	No reaction	No reaction

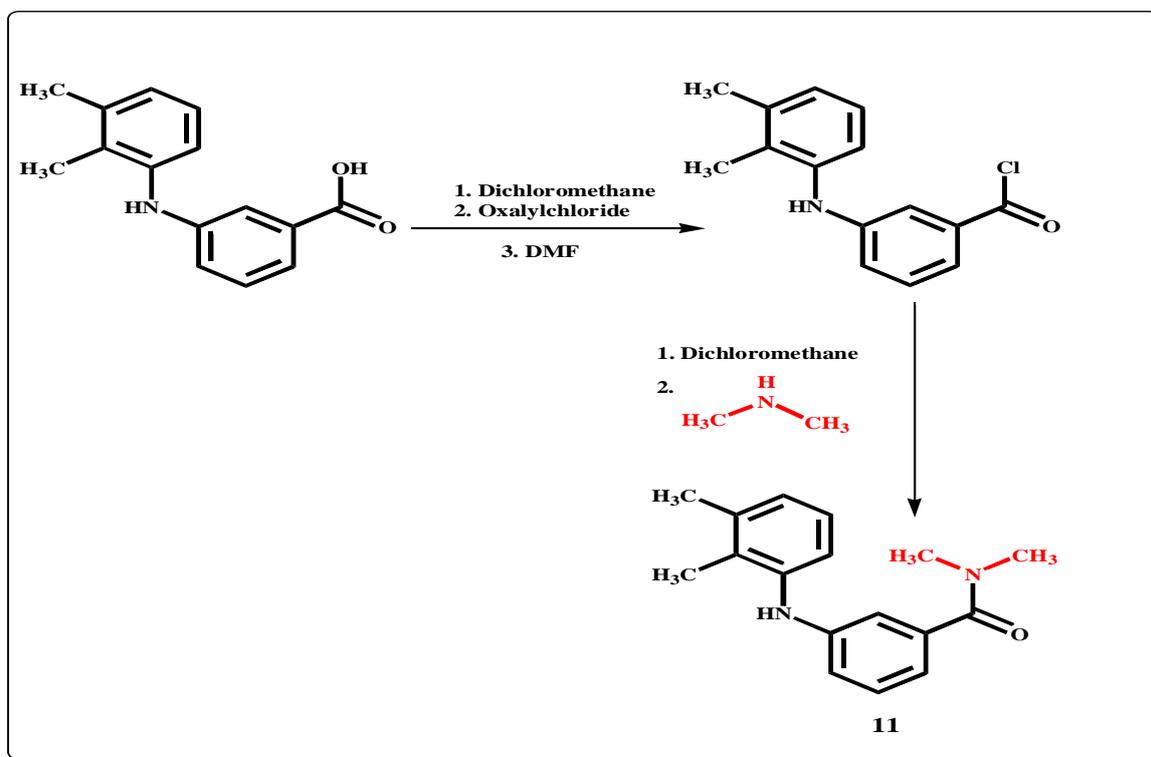


Figure 5: Synthesis pathway for tranexamic acid- N,N-Dimethylamide prodrug, 11

Table 2: Hydrolysis of prodrug 11 at different pHs

Medium	K_{obs} (h^{-1})	$t_{1/2}$ (h)
1N HCl	1.14×10^{-4}	11.4
Buffer pH 2.5	No reaction	No reaction
Buffer pH 5.5	No reaction	No reaction
Buffer pH 7.4	No reaction	No reaction

SUMMARY & CONCLUSIONS

In this mini review we have succeeded to cover most of mefenamic acid prodrugs and codrugs which have been synthesized during the past twenty years with the aim to provide molecules having the same anti-inflammatory and analgesic activity of mefenamic acid, but

lacking the gastrointestinal adverse effects associated with the use of NSAIDs in general and mefenamic acid in particular.

Most of the mefenamic acid prodrugs and codrugs described in this mini-review were synthesized by the classic prodrug approach, by which the active parent drug is attached to a promoiety or another active drug directly or via a spacer which upon exposure to physiological environment undergoes an enzymatic catalyzed cleavage and releases the active parent drug. This approach involves enzyme catalysis which has many disadvantages due to many intrinsic and extrinsic factors that can affect the process. For instance, the activity of many prodrug-activating enzymes may be varied due to genetic polymorphisms, age-related physiological changes, or drug interactions, leading to variation in clinical effects. Therefore, there is a need to develop prodrugs that have the potential to undergo interconversion to their parent drugs via intramolecular reaction and without the need for enzyme catalysis. The modern computational approach which has been utilized by Karaman's group considers attaching a designed linker to an active drug, such as NSAIDs, that has poor bioavailability and/or toxic side effects, and releasing the parent drug via intramolecular chemical reaction without the involvement of metabolic enzymes. With the possibility of designing prodrugs with different linkers, the release rate of the parent drug can be controlled and the disadvantages associated with the metabolic enzymes will be eliminated.

Advances must be made in understanding the chemistry of many organic reactions that can be effectively utilized to enable the development of even more types of prodrugs. The understanding of organic reaction mechanisms of certain processes, particularly intramolecular reactions, will be the next major milestone in the field of prodrug design and development.

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