WORLD JOURNAL OF PHARMACY AND PHARMACEUTICAL SCIENCES
SJIF Impact Factor 5.210
Volume 4, Issue 07, 1960-1982. Review Article ISSN 2278 – 4357

DICLOFENAC CODRUGS AND PRODRUGS-THREE DECADES OF DESIGN

khuloud Dweib[1], Salma Jumaa[1], Ameen Thawabteh[1,3], Laura Scrano[2], Sabino A. Bufo[3], [4]Gennaro Mecca, Rafik Karaman*[1,3]

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

[2]Department of European Cultures (DICEM), University of Basilicata, Via dell'Ateneo Lucano 10, Potenza 85100, Italy.

[3]Department of Sciences, University of Basilicata, Viadell'Ateneo Lucano 10, 85100, Potenza, Italy.

[4]Exo Research Organization, Potenza, Italy.

Article Received on
17 May 2015,

Revised on 08 June 2015,
Accepted on 29 June 2015

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

ABSTRACT

Prodrugs or predrugs are inactive molecules which become active after *in vivo* conversion to release the active parent drug. The prodrug's cleavage can be catalyzed by metabolic enzymes or can occur by chemical means without the involvement of enzymes. Prodrugs are designed to improve undesirable physicochemical and pharmacokinetic properties of their parent drugs. Non-steroidal anti-inflammatory (NSAIDs) drugs are among the most commonly used drugs for treatment of pain, inflammation and fever. Despite their frequent use, these agents suffer from gastrointestinal side effects that limit their use for those patients with gastrointestinal conditions. This mini review discusses the design, synthesis and pharmacological effects of prodrugs and codrugs of the non-steroidal anti-inflammatory (NSAIDs) Diclofenac sodium or potassium. It argues that the prodrug approach has the potential to eliminate Diclofenac associated gastrointestinal complications, increases its bioavailability and masks its bitter taste.

KEYWORDS: Non-steroidal anti-inflammatory drugs, gastrointestinal complications, enzymatic biotransformation, Diclofenac, Prodrugs, Predrugs.

Prodrugs are molecules which are converted *in vivo* to their parent active drugs by enzymatic or chemical transformation to give theraputic effect.[1-2] Prodrugs have many advantages over their parent drugs, they are designed to improve the physicochemical and pharmacokinetic properties of their parent active drugs and hence to an improvement in their oral absorption, aqueous solubility and bioavailability and a reduction in their toxicity and/or bitter sensation.[2-3]

Historically, prodrugs of chloramphenicol were the first to be synthesized by Davis Company. The company's goal was to make more water soluble derivatives such as chloramphenicol sodium succinate, and bitterless derivatives such as chloramphenicol palmitate.[4-5]

Prodrugs are classified into two classes: (1) carrier linked prodrugs, in which the active drug is linked covalently to a nontoxic linker; the cleavage of the linkage in this class occurs by uncatalyzed or enzyme catalyzed chemical reaction to provide the active parent drug. The non-toxic linker is then excreted out the body.[6] This class is divided into three subclasses: (i) bipartite which consists of one linker; (ii) tripartite, which has a spacer connecting the drug and linker and (iii) mutual prodrugs, which consist of two drugs attached together. (2) bioprecursor prodrugs, which themselves do not have any therapeutic effect until they undergo *in vivo* metabolism to metabolites having therapeutic effects.[7]

Since 1960, prodrug design has become much more popular which consequently resulted in promoting and progressing the drug discovery and development field.[8] Recent statistical studies showed that about 10% of all marketed drugs worldwide are prodrugs. In 2008 alone, about 33% of all approved small-molecular-weight medications were prodrugs. In 2009, about 15% of the 100 highest selling small molecular-weight drugs were prodrugs.[1, 9]

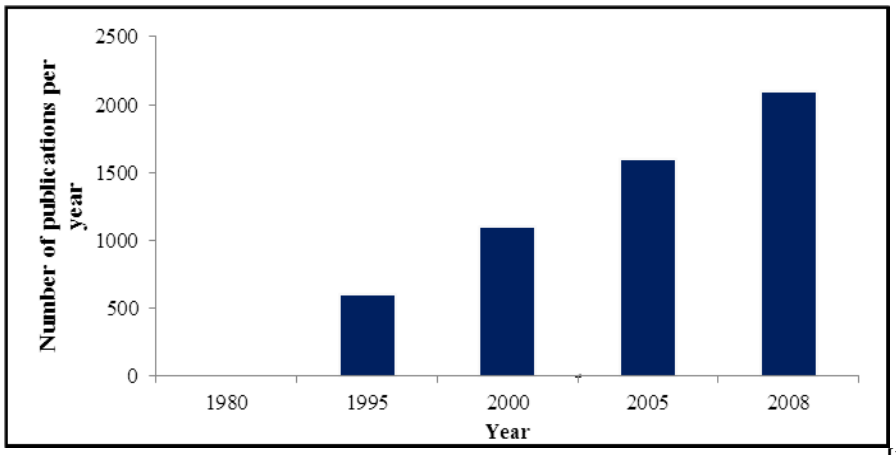

Figure 1: Number of publications for prodrugs found in Scifinder.[1]

Non-steroidal anti-inflammatory drugs (NSAIDs) are considered as the best treatment for conditions associated with pain, fever and inflammation.[10] Several epidemiological reports have indicated that non-steroidal anti-inflammatory agents have shown to play a role in inhibiting cancerous cells and some of these drugs have even showed positive results in human studies.[11]

Diclofenac is a non-steroidal anti-inflammatory drug (NSAID), which has a strong analgesic and anti-inflammatory effect. Tablets and suppositories of Diclofenac are prescribed for fever, pain relief and chronic inflammatory diseases such as osteoarthritis.[12-13]

Diclofenac like other non-steroidal anti-inflammatory drugs exerts its therapeutic effect by blocking prostaglandin synthesis from arachidonic acid, which inhibits the activity of cyclooxygenases (COX-1 and COX-20.[14] COX-1 is located in the stomach, kidney, and other tissues, while COX-2 is located at inflammation sites.[15-16]

Although the NSAIDs are the most used class of drugs throughout the world (in 2009, their sale benefit was more than $9 billion),[17] NSAIDs use can cause severe stomach problems including hemorrhaging, ulceration, and cardiovascular side effects. These complications may cause withdrawal cases in patients under NSAIDs treatment.[18] A study report on 'Toxic and Deadly NSAIDs', stated that NSAID gastrointestinal side effects on arthritis patients resulted in about 107,000 hospitalization cases and about 16,500 deaths per year in the United States, alone.[17]

Classical NSAIDs, such Diclofenac, inhibit COX-1 activity and block the biosynthesis of prostaglandins that protect the gastric mucosa, they also cause local irritation by the free carboxylic acid contained in their structures. Both factors are the source for the gastrointestinal complications resulted from the use of NSAIDs.

It is widely believed that eliminating the gastrointestinal side effects and reducing the toxicity associated with the NSAIDs use can be achieved *via* chemical modifications of the main functional groups contained in the NSAID structure.[19]

These chemical modifications include: (1) ester and amide prodrug derivatives: ester prodrugs are synthesized by reacting the carboxylic group of the NSAID with an alcohol. On the other hand, amide prodrugs are made by the reaction of the carboxylic group of the NSAID (*via* an acyl halide) with an amine. The hydrolysis reactions for ester and amide

prodrugs are generally catalyzed by enzymes, esterases for ester hydrolysis and amidases for amide hydrolysis. (2) Anhydride prodrugs of NSAIDs: these are synthesized by a reaction of the carboxylic group of the NSAID with another carboxylic group. Generally, the anhydride linkage is more labile to hydrolysis than the ester and amide linkages, and undergoes cleavage to the corresponding carboxylic acid (the NSAID parent drug) in a controlled manner.[20] (3) Mutual prodrugs are two active drugs that are linked to each other by a covalent bond to furnish a single inactive moiety that is enzymatically or chemically converted to the active parent drugs[21] and (4) amino acids and 5- glucosamine conjugate prodrugs of NSAIDs.

In 1993, morpholinoalkyl esters of Diclofenac (Figure 2) were synthesized and their hydrolysis, in phosphate buffer pH 7.4 and plasma of rats, was evaluated. The prodrugs were found to have better absorption than their parent drug and they underwent cleavage in fast rates. In addition, the study showed that *in vivo* irritation of gastrointestinal mucosa of rat was significantly lower using these prodrugs compared to that after a single and chronic oral administration of Diclofenac (the active parent drug).[22]

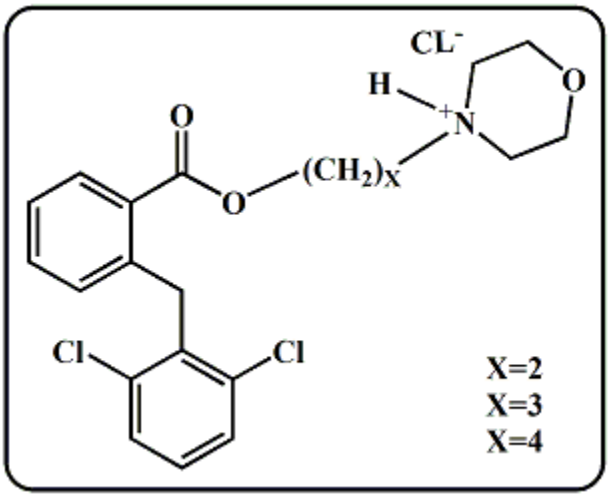

Figure 2: Chemical structure of morpholinoalkyl Diclofenac ester prodrugs.

Tabrizi and coworkers have made several Diclofenac prodrugs by attaching Diclofenac to polychloromethylstyrene, polyvinyl chloroacetate and polyethylene glycol through a labile ester bond. The group found that polymers are useful as polymeric prodrugs while the polyvinyl chloroacetate was evaluated as a good carrier for *in vivo* release of the drug. The hydrolysis of polymer-drug conjugates in cellophane membrane dialysis bags containing buffer solutions pH 8 at 37 Cº was studied and the rate of the hydrolysis was determined.

However, no sharp results were obtained and further study should be undertaken to draw conclusions on the feasibility of using these prodrugs in human.[23]

In 1996, several NSAIDs such as Ibuprofen, Naproxen, Diclofenac and Ketorolac were reacted with R-(-)-2-amino-1-butanol with the aim of providing the corresponding amide prodrugs with better bioavailability and less gastrointestinal side effects. The analgesic activity and toxicity of the synthesized prodrugs were investigated and compared to that of the corresponding active parent drugs.[24]

In 1997, Jilani *et al.* has synthesized hydroxyethyl esters of Diclofenac and Mefenamic acid aiming to provide NSAIDs prodrugs with efficient analgesic activity and lesser gastrointestinal side effects than their active parent drugs. Stability study on those prodrugs was conducted in 1N HCl, buffer solutions of pH 7.4 and human plasma. The hydrolytic degradation rate of the Diclofenac ester in aqueous buffer solutions was very slow with a half-life of more than 22 hours, whereas the degradation rate in human plasma was very fast with a half-life value of less than 1.2 hours. This indicates that the Diclofenac prodrug is quite stable in the stomach conditions and hence it is expected that its gastrointestinal side effects will be lesser than that of Diclofenac due to masking the free carboxylic group in Diclofenac, which is believed to be responsible in part for these adverse effects.[25]

In 1999, Mahfouz *et al.* has conducted ulcerogenicity study, using electron microscopy on rat's stomach; the rats were treated for 4 days with the synthesized NSAIDs ester prodrugs before the ulcerogenicity test. The study revealed that the synthesized prodrugs have shown lesser irritation to the stomach's mucosa than their active parent drugs.[26]

In 2000, Bandarage and coworkers synthesized Diclofenac ester prodrugs containing a nitrosothiol (S-NO) group aiming to provide NSAIDs with the capability to donate N-O group. These prodrugs were orally administered to mice for bioavailability and toxicity evaluation. The study demonstrated that those prodrugs released the active parent drug, Diclofenac, in a significant amount within 15 minutes and showed an efficient inflammatory effect. The S-NO Diclofenac prodrugs illustrated in Figure 3 were shown to be much safer than their active parent drug, Diclofenac. In addition, the study demonstrated that rat stomach lesions caused by S-NO-diclofenac derivatives were less than lesions caused by the parent drug, Diclofenac.[27]

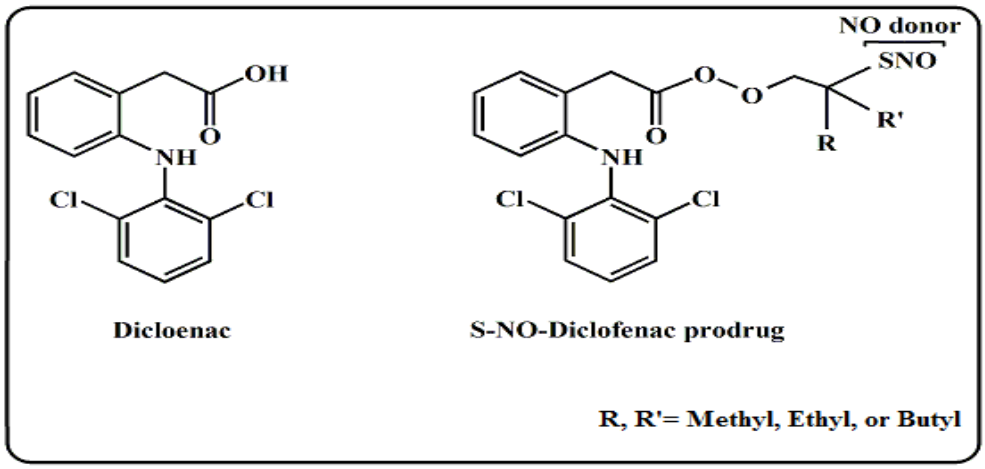

Figure 3: Chemical structures of Diclofenac and its S-NO prodrugs.

In 2000, Seung and coworkers have made several alkyl ester prodrugs of Diclofenac, and studied their physicochemical properties such as solubility, partition coefficients, pKa and stability in aqueous buffered solutions and in human plasma. The permeation study of the synthesized prodrugs across hairless mouse skin indicated that the methyl and ethyl prodrug derivatives were found to have higher lipid solubility, log P, of 5.5 and 5.1 at pH 7.0, respectively, when compared with their parent drug, Diclofenac. In addition, their study revealed that the prodrugs showed moderate chemical stability in aqueous solutions at different pHs, except strong acidic and basic conditions, and underwent enzyme catalyzed-hydrolysis to their parent drug in human plasma. Further, the prodrugs demonstrated a higher flux across the hairless mouse skin than their parent drug (2.6-fold of their parent drug). The prodrugs lag time and solubility were found to be lesser than Diclofenac and their pKa values were in the range of 6.9 and 7.2.[28]

In 2002, Hirabayashi and coworkers have carried out a study on *in vivo* disposition at whole body, organ and cellular levels of bisphosphonic prodrug of Diclofenac (DIC-BP) (Figure 4) upon administration of a dose in the range of 0.32-10 mg/kg. Their study indicated that both total body clearance and volume of distribution at steady state were reduced while the plasma half-life was prolonged. In addition, the study revealed that more than 50% of DIC-BP was transported into osseous tissues when was given in a dose of up to 1mg/kg, however when the dose was increased the skeletal distribution was decreased and both hepatic and splenic accumulations were increased. This is because bisphosphonates cannot be distributed in tissues but they can form a large complex with endogenous metals in plasma and are recognized as foreign substances from macrophages and thus being taken by the

reticuloendothelial system. In order to optimize the DIC-BP prodrug's delivery, the dosage regimen should be such that the plasma concentration of DIC-BP is maintained at a level lower than that required for precipitate complexes, similar to that of other bisphosphonates.[29]

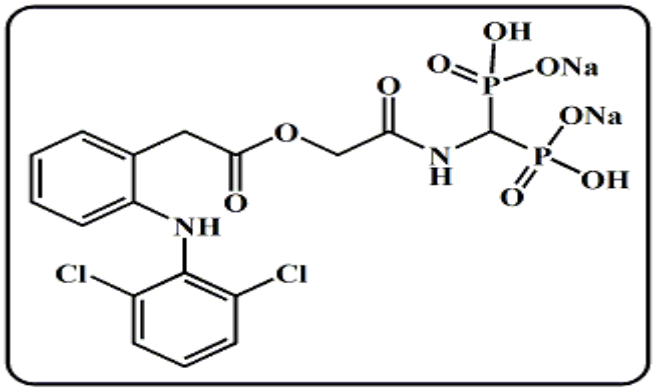

Figure 4: Chemical structure of Diclofenac bisphosphonic prodrug.

In 2004, Dalpiaz and coworkers have studied the *in vitro* intracellular uptake of Diclofenac and its conjugate ascorbic acid (AA-Diclo) (Figure 5) and their affinity for the SVCT2 transporter. In addition, the AA-Diclo prodrug stability was investigated. The hydrolysis study followed a first-order kinetics with a half-life of about 10 hours in plasma and about 3 hours in the whole blood, suggesting that AA-Diclo prodrug is a potential candidate to enhance the short half-life of Diclo *in vivo.*[30]

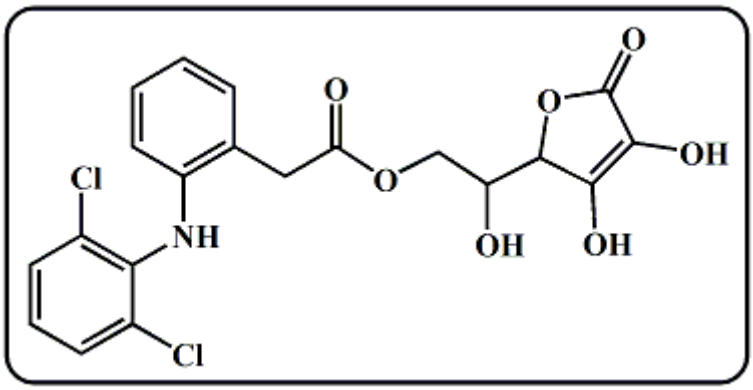

Figure 5: Chemical structure of AA-Diclo prodrug.

In 2004, Khan and coworkers have synthesized a number of glyceride derivatives of Diclofenac and have studied their gastrointestinal side effects, anti-inflammatory and analgesic activity. In addition, the group has investigated the release of the active parent drug from these prodrugs in a wide range of pHs. Their results revealed that the synthesized

glyceride prodrugs were found to lack any gastrointestinal side effects and their analgesic and anti-inflammatory effects were significantly greater than that of the active parent drug, Diclofenac.[31]

In 2009, Manon *et al.* has synthesized a number of Diclofenac-antioxidant mutual prodrugs by conjugating Diclofenac with different antioxidants having anti-ulcerogenic activity. The study screening revealed that the synthesized mutual prodrugs retained the anti-inflammatory activity as Diclofenac however with lesser ulcerogenic side effects.[32]

In 2010, Nemmani *et al.*, has designed, synthesized and evaluated new NO-releasing NSAID prodrugs such as NO-Aspirin and NO-Diclofenac (Figure 6). NO-Diclofenac showed excellent pharmacokinetic, anti-inflammatory properties. In addition, this prodrug showed significant NO-releasing properties and protected rats from NSAID-induced gastric damage which could be attributable to the beneficial effects of NO released from this prodrug [33].

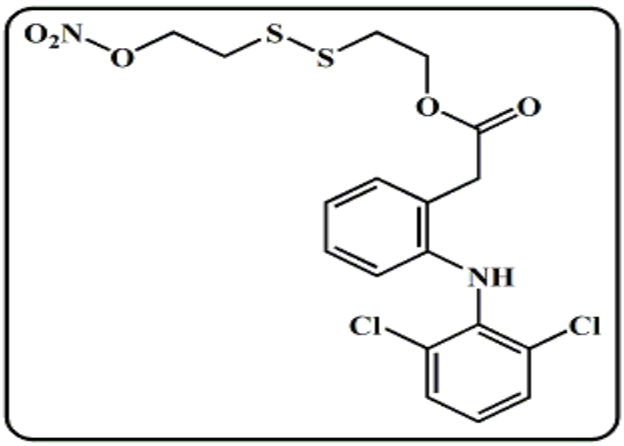

Figure 6: Chemical structure of NO-Diclofenac prodrug.

In 2011, Diclofenac ester prodrugs **1-3** (Figure 7) were synthesized and their *in vitro* and *in vivo* pharmacokinetic and pharmacodynamics properties were evaluated. A study which conducted after oral administration of ester prodrugs, **1-3** revealed that these compounds have a very good analgesic and anti-inflammatory activity with lesser gastrointestinal irritation than their active parent drug, Diclofenac, and they underwent a rapid enzymatic hydrolysis to their parent drug.[34, 35]

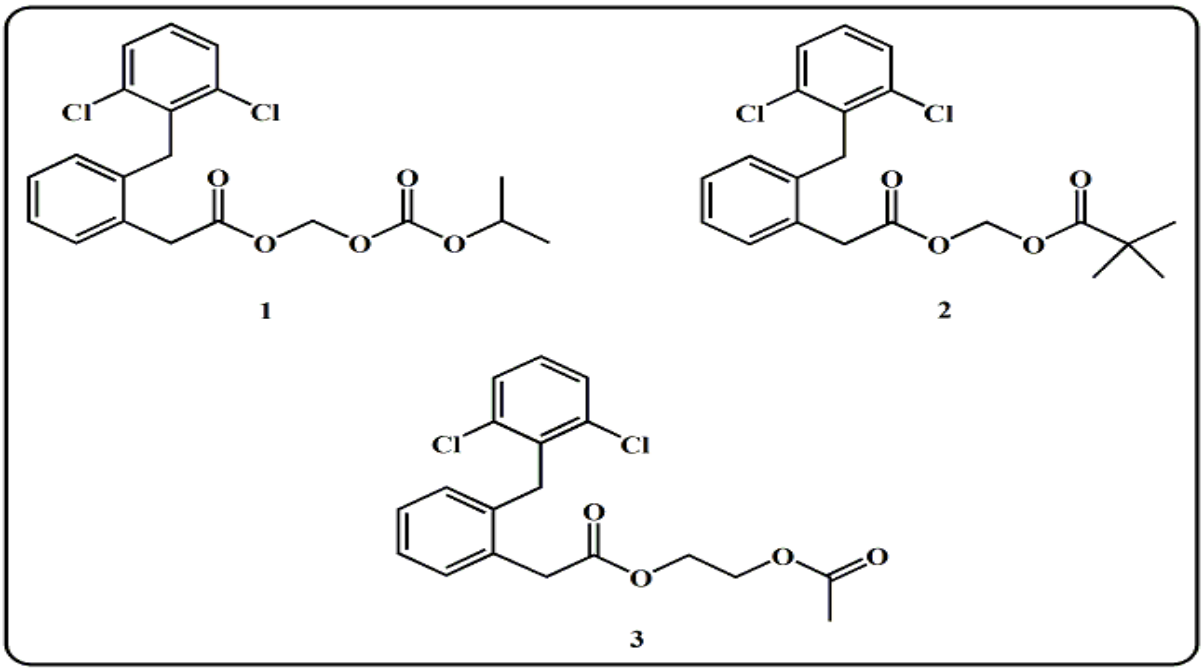

Figure 7: Chemical structures of Diclofenac ester prodrugs 1-3.

In 2012, Santos *et al.* has synthesized 1-(2,6-dichlorophenyl)indolin-2-one, a Diclofenac prodrug, and studied its therapeutic activity. The study demonstrated that the new prodrug has shown relevant anti-inflammatory properties without gastrointestinal side effects. Furthermore, the study showed that the prodrug decreased PGE2 levels, COX-2 expression and cellular influx into peritoneal cavity induced by carrageenan treatment. The pharmacokinetic studies on the prodrug have shown *in vivo* enzyme catalyzed interconversion of the prodrug to its parent active drug, Diclofenac. Santos *et al.* has concluded based on this study that the synthesized new nonulcerogenic NSAID prodrug is useful to treat inflammatory conditions by long-term therapy.[36]

In 2012, Ghosh *et al*. has synthesized four codrugs of Naltrexone and Diclofenac linked together *via* phenolic or alcoholic linker. Transdermal flux, permeability and skin concentration of both parent drugs and codrugs were quantified to form a structure permeability relationship. The results revealed that all codrugs underwent bioconversion in the skin. The extent of the bioconversion was found to be dependent on the structure; phenol linked codrugs were less stable compared to the secondary alcohol linked ones. The flux of Naltrexone across microneedle treated skin and the skin concentration of Diclofenac were higher for the phenol linked codrugs. The polyethylene glycol link enhanced solubility of the codrugs, which translated into flux enhancement. Based on the study results, Gosh *et al.*

concluded that polyethylene glycol linked Naltrexone diclofenac codrug is better suited for a 7 day drug delivery system both in terms of stability and drug delivery.[37]

In 2014, Dhurgham *et al.* has synthesized codrugs of NSAIDs, Indomethacin and Diclofenac, linked to the anticancer drug Gemcitabine (Figure 8). The synthesized codrugs showed improved drug targeting for Gemcitabine, reduced stomach side effects of NSAIDs by masking their carboxylic acid group and increased their oral bioavailability because COX-2 is expressed in cancerous cells more than normal tissue, so the mutual prodrug will specifically and efficiently target the cancerous cells.[38]

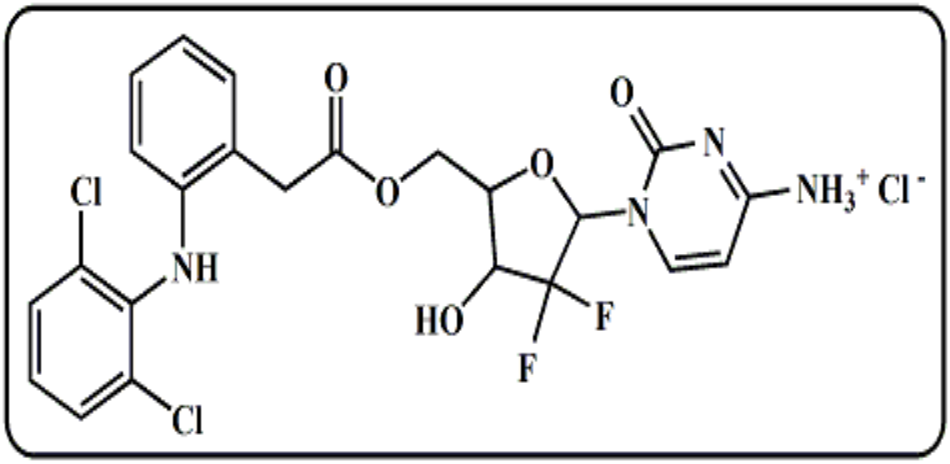

Figure 8: Diclofenac–Gemcitabine conjugate

In 2013, Suryawanshi *et al*. has synthesized five Diclofenac ester prodrugs (Figure 9) by reacting the corresponding alcohol with the NSAID drug aiming at reducing the undesired side effects, the most important being gastrointestinal (GI) irritation and ulceration, associated with the use of NSAIDS. It is widely believed that using the prodrug approach by temporary blocking the free carboxylic group present in the NSAIDs till their systemic absorption, is the best way to retain the anti-inflammatory effect of the NSAID and eliminate all gastrointestinal adverse effects associated with its use. All five Diclofenac ester prodrugs were evaluated for anti-inflammatory activity by Carrageenan Induced Rat hand Paw method and all of the prodrugs without exception showed quite appreciable anti-inflammatory activity.[39]

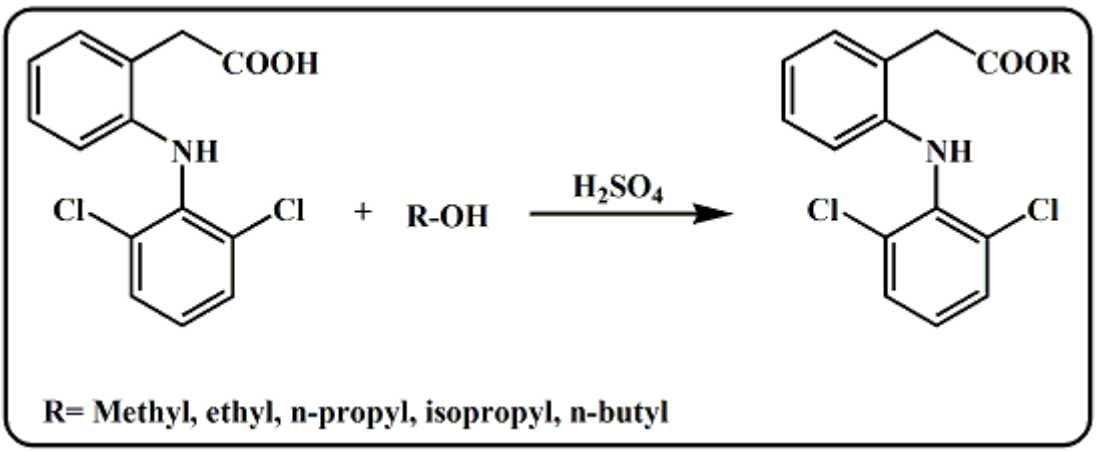

Figure 9: Ester prodrugs of Diclofenac.

Bhosle and coworkers have synthesized prodrugs and codrugs of NSAIDs with glucosamine to mask the carboxylic group of the NSAID in order to decrease its gastrointestinal side effects. Glucosamine is an amino sugar, used by human body to produce endogenous joint molecules like joint lubricants. Glucosamine hydrochloride and sulphate are being used to treat arthritis. The synthesized mutual prodrug of Diclofenac coupled with D-glucosamine illustrated in Figure 10 demonstrated a reduction in gastrointestinal irritation and an increase in the analgesic and anti-inflammatory effects. In addition, it has demonstrated a quite fair anti-arthritic activity.[40]

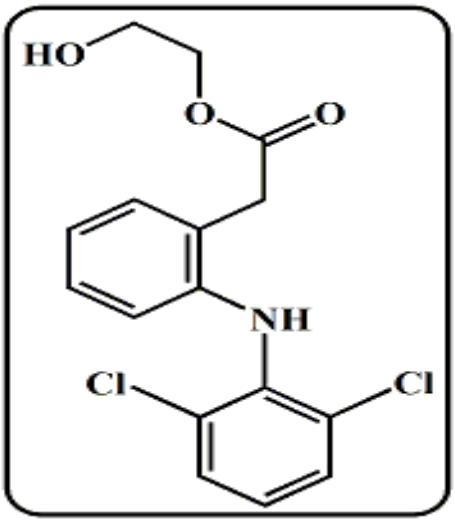

Figure 10: Diclofenac D-glucosamine prodrug.

In 2014, Hasan *et al.* has synthesized eight Diclofenac-Chalcone mutual prodrugs aiming to provide anti-inflammatory agents with enhanced anti-inflammatory activity and less ulcerogenic adverse effects than their parent drugs. The mutual prodrugs were synthesized by

conjugation of Diclofenac with Chalcone derivatives by the Claisen–Schmidt condensation of acetophenone or p-hydroxy acetophenone with benzaldehyde or appropriately substituted benzaldehyde in the presence of a catalyst. The anti-inflammatory activity of the synthesized fluorinated Chalcone derivative was performed using the cotton pellet-induced granuloma in rats as a model, and found to be comparable to that of Dexamethasone. Based on this study, Hasan *et al.* has concluded that chalcones with their pronounced anti-inflammatory activity can synergize the activity of Diclofenac when both are in the same compound (codrug).[41]

The classical prodrug approach requires the involvement of an enzyme for the interconversion of a prodrug to its active parent drug. On the other hand, enzyme catalysis has many disadvantages as a result of many intrinsic and extrinsic factors that can affect the interconversion rate. For example, prodrug-activating enzymes activities are largely varied due to genetic polymorphisms, age-related physiological changes, or drug interactions, resulting in flocculation in drugs' clinical profiles. Hence, it is necessary to make prodrugs having the potential to intraconvert to their active parent drugs through an intramolecular process in the absence of enzyme catalysis.[42-44]

In the past 6 years we have been studying the mechanisms of a number of intramolecular processes which were advocated by others aiming to find chemical devices, mimicking enzymes, which could shed light on how enzyme catalyze biotransformations. On our side we have exploited these enzyme models in a novel prodrug chemical approach by which the linker (enzyme model) is attached to an active moiety (parent drug) such that the active drug's release rate from the prodrug moiety will be solely dependent on the structural features of the linker.

Using molecular quantum and molecular mechanics methods we have designed several prodrugs for commonly used drugs suffering from low bioavailability, low water solubility, bitter sensation and/or other drawbacks.[45-99]

For instance, exploring the mechanism of Kirby's acetals using DFT methods revealed to the design and synthesis of novel prodrugs that intraconvert to their parent drugs in the absence of enzymes. Among those are prodrugs of the anti-myelodysplastic aza-nucleosides,[89] anti-malarial atovaquone,[90-92] anti-cholesterol agents, statins[93] and the decongestant, phenylephrine.[94] In these cases, the hydroxyl group of the active parent drug was covalently linked to Kirby's enzyme model (linker) such that the drug-promoiety (prodrug) has the potential to undergo cleavage upon exposure to physiological environments such as stomach,

intestine, and/or blood circulation, with rates that are solely determined by the structural features of the pharmacologically inactive linker (Kirby's enzyme model).[55-59, 65]

Moreover, prodrugs aiming to eliminate the bitterness of the pain killer paracetamol, the anti-hypertensive atenolol and the antibiotics, cefuroxime, amoxicillin and cephalexin were designed and synthesized.[45-50] The role of the linker in these prodrugs is to block the free hydroxyl or amine group, which is believed to be responsible for the drug's bitter sensation.[84-86, 96-97] Prodrugs of the anti-Parkinson disease, dopamine, were designed and synthesized *via* linking the active parent drug with Menger's Kemp acid enzyme model.[87] Similarly, dimethyl fumarate prodrugs were designed and made for the treatment psoriasis.[88]

Exploring the mechanism of Kirby's N-alkylmaleamic acids (enzyme model) has led to the design and synthesis of a respected number of prodrugs of the following commonly used drugs: the anti-bleeding agent, tranexamic acid,[82] the anti-viral acyclovir,[83] the anti-hypertensive agent, atenolol.[84-85]

Continuing our investigations on how to use the enzyme models that their mechanisms were computationally unraveled we have utilized the acid-catalyzed hydrolysis of N-alkyl maleamic acids (Kirby's enzyme model)[59] to design and synthesize codrugs and prodrugs of Diclofenac and Tranexamic acid. Our goal was to provide drugs and codrugs of Diclofenac with relatively good anti-inflammatory and analgesic activities but with less gastrointestinal adverse effects. Additionally, codrugs containing tranexamic acid in which the amine group of this acid is replaced with an amide, has the potential to be more permeable and hence more bioavailable than Tranexamic acid.

Prodrug and codrugs of Diclofenac were synthesized by the reaction of the acyl chloride of Diclofenac with either Tranexamic acid (Figure 11) or benzylamine (Figure 12). Kinetic studies on both compounds were carried out at different pHs and at 37℃, and monitored by HPLC. The kinetic results for the codrug and prodrug are listed in Tables 1 and 2, respectively.

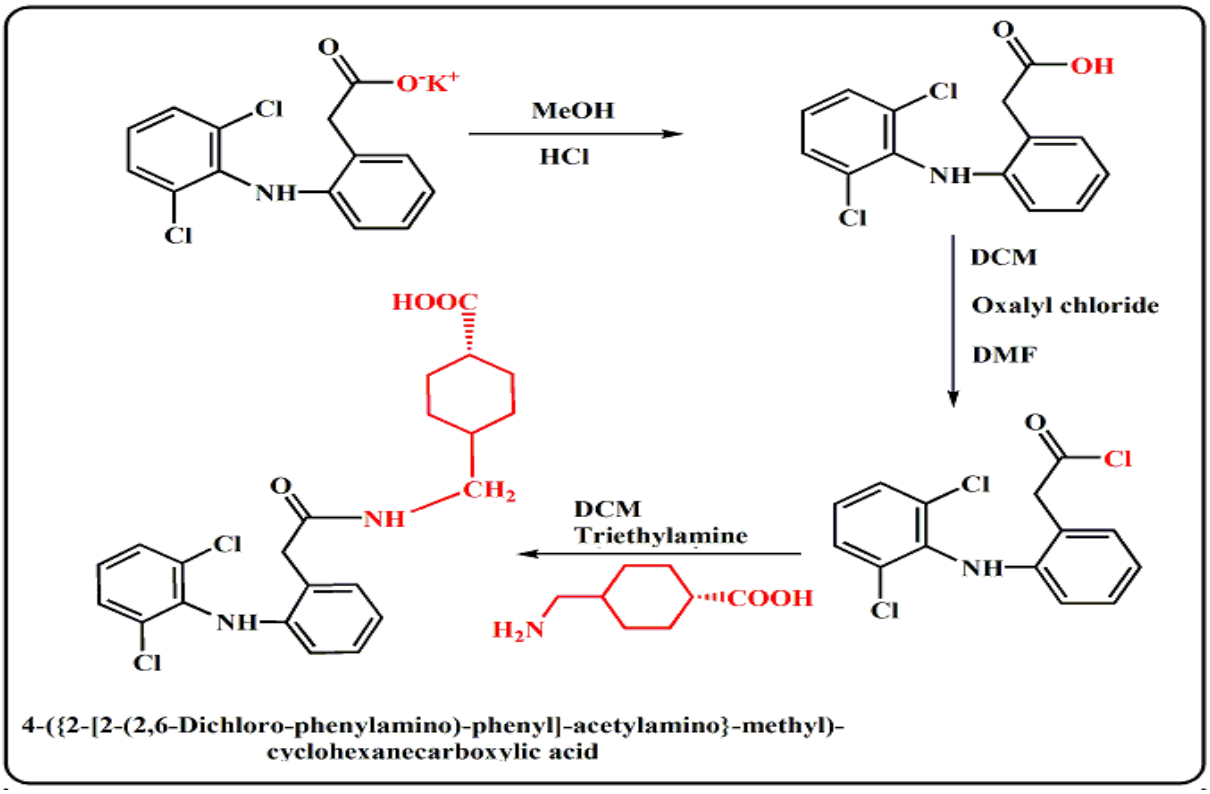

Figure 11: Schematic diagram for the synthesis of Diclofenac-Tranexamic acid codrug.

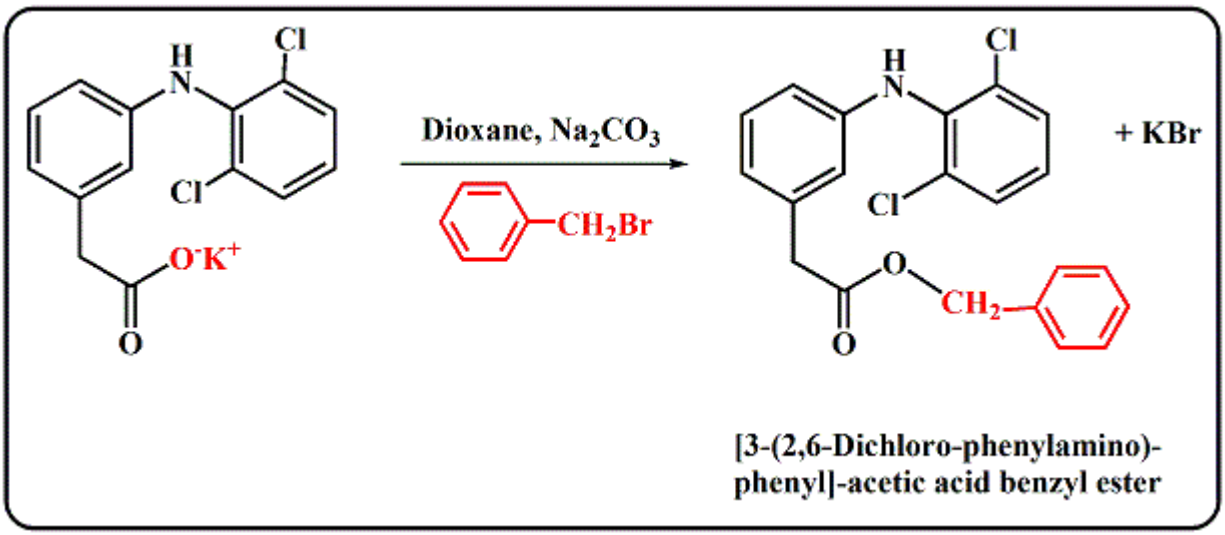

Figure 12: Schematic diagram for the synthesis of Diclofenac-benzyl amide prodrug.

Table 1: Kinetics parameters for the hydrolysis of diclofenac-tranexamic acid codrug

Medium	$t_{½}$ (h)
1N HCl	**32.4**
Buffer pH 2.5	No reaction
Buffer pH 5.5	No reaction
Buffer pH 7.4	No reaction

Table 2: Kinetics parameters for the hydrolysis of diclofenac-benzyl amide prodrug.

Medium	$t_{½}$ (h)
1N HCl	**10**
Buffer pH 2.5	No reaction
Buffer pH 5.5	No reaction
Buffer pH 7.4	**11**

SUMMARY AND CONCLUSIONS

This mini review contains most of diclofenac prodrugs and codrugs prepared in the past twenty years and a comprehensive description of the different approaches to decrease diclofenac gastrointestinal side effects.

Most of the reported prodrugs and codrugs have shown to undergo biotransformation by enzymatic catalysis. The latter has many disadvantages because prodrug-activating enzymes can vary from person to person due to age or drug and food interaction, which can cause variation in clinical effects. Therefore, it is necessary to make prodrugs that have the ability to undergo inter- or intraconversion to their parent drugs without the involvement of metabolic enzymes such as esterases and amidases.

The computational approach, which has been recently utilized by Karaman's group, considers linking a nontoxic linker to an active drug, such as NSAIDs, that has poor bioavailability or suffers from gastrointestinal adverse effects. In Karaman's approach, the prodrug undergoes an intramolecular cleavage to furnish the active parent drug without the need to enzyme catalysis. Different linkers can be attached to the drug and the rate of the active drug's release can be determined upon the structural features of the linker attached to the drug. By this approach, the release of the parent drug from its prodrug can be controlled and the variation of clinical effects that might be caused by the enzyme catalysis will be prevented.

REFERENCES

1. Müller, C. E. (2009). Prodrug approaches for enhancing the bioavailability of drugs with low solubility. Chemistry & Biodiversity, 6(11): 2071-2083.
2. Yang, Y. H., Aloysius, H., Inoyama, D., Chen, Y., & Hu, L. Q. (2011). Enzyme-mediated hydrolytic activation of prodrugs. Acta Pharmaceutica Sinica B, 1(3): 143-159.
3. Zawilska, J. B., Wojcieszak, J., & Olejniczak, A. B. (2013). Prodrugs: a challenge for the drug development. Pharmacological Reports, 65(1): 1-14.

4. Stella, V., Borchardt, R., Hageman, M., Oliyai, R., Maag, H., & Tilley, J. (Eds.). (2007). Prodrugs: challenges and rewards. Springer Science & Business Media.
5. Glazko, A. J., Carnes, H. E., Kazenko, A., Wolf, L. M., & Reutner, T. F. (1956). Succinic acid esters of chloramphenicol. Antibiotics annual, 5: 792-802.
6. Jana, S., Mandlekar, S., & Marathe, P. (2010). Prodrug design to improve pharmacokinetic and drug delivery properties: challenges to the discovery scientists. Current medicinal chemistry, 17(32): 3874-3908.
7. Roche, E. B. (1977). Design of biopharmaceutical properties through prodrugs and analogs: a symposium. Amer Pharmacutical Assn.
8. Van De Waterbeemd, H., Smith, D. A., Beaumont, K., & Walker, D. K. (2001). Property-based design: optimization of drug absorption and pharmacokinetics. Journal of medicinal chemistry, 44(9): 1313-1333.
9. Huttunen, K. M., Raunio, H., & Rautio, J. (2011). Prodrugs—from serendipity to rational design. Pharmacological reviews, 63(3): 750-771.
10. Mehta, N., Aggarwal, S., Thareja, S., Malla, P., Misra, M., Bhardwaj, T. R., & Kumar, M. (2010). Synthesis, pharmacological and toxicological evaluation of amide derivatives of ibuprofen. International Journal of Chem Tech Research, 2(1): 233-238.
11. Wakabayashi, K. (2000). NSAIDs as cancer preventive agents. Asian Pac J Cancer Prev, 1(2): 97-113.
12. Lobo, S., Li, H., Farhan, N., & Yan, G. (2014). Evaluation of diclofenac prodrugs for enhancing transdermal delivery. Drug development and industrial pharmacy, 40(3): 425-432.
13. Nazeruddin, G. M., & Suryawanshi, S. B. (2010). Synthesis of Novel Mutual Pro-drugs by coupling of Ibuprofen (NSAID) with Sulfa drugs. J. Chem. Pharm. Res, 2(4): 508-512.
14. Flower, R. J., & Blackwell, G. J. (1979). Anti-inflammatory steroids induce biosynthesis of a phospholipase A2 inhibitor which prevents prostaglandin generation.
15. Willoughby, D. A., Moore, A. R., & Colville-Nash, P. R. (2000). COX-1, COX-2, and COX-3 and the future treatment of chronic inflammatory disease. The Lancet, 355(9204): 646-648.
16. Vane, J. R., & Botting, R. M. (1998). Mechanism of action of nonsteroidal anti-inflammatory drugs. The American journal of medicine, 104(3): 2S-8S.
17. Melnikova, I. (2010). Pain market. Nature Reviews Drug Discovery, 9(8): 589-590.
18. Nemmani, K. V., Mali, S. V., Borhade, N., Pathan, A. R., Karwa, M., Pamidiboina, V., ... & Satyam, A. (2009). NO-NSAIDs: Gastric-sparing nitric oxide-releasable prodrugs of

non-steroidal anti-inflammatory drugs. Bioorganic & medicinal chemistry letters, 19(18): 5297-5301.

19. Warner, T. D., Giuliano, F., Vojnovic, I., Bukasa, A., Mitchell, J. A., & Vane, J. R. (1999). Nonsteroid drug selectivities for cyclo-oxygenase-1 rather than cyclo-oxygenase-2 are associated with human gastrointestinal toxicity: a full in vitro analysis. Proceedings of the National Academy of Sciences, 96(13): 7563-7568.
20. Makhija, D. T., & Somani, R. S. (2010). Improvement of GI tolerance of NSAIDs using oral prodrug approach. Der Pharmacia Lett, 2: 300-9.
21. Strasinger, C. L., Scheff, N. N., & Stinchcomb, A. L. (2008). Prodrugs and codrugs as strategies for improving percutaneous absorption.
22. Tammara, V. K., Narurkar, M. M., Crider, A. M., & Khan, M. A. (1994). Morpholinoalkyl ester prodrugs of diclofenac: synthesis, in vitro and in vivo evaluation. Journal of pharmaceutical sciences, 83(5): 644-648.
23. Tabrizi, M. N., Davaran, S., & Entezami, A. (1996). Synthesis of diclofenac polymeric prodrugs and their hydrolysis reactivity. Iran Polym J, 5(4): 243-251.
24. Akgün, H., Tozkoparan, B., Ertan, M., Aksu, F., & Inan, S. Y. (1996). Synthesis of some 2-arylpropionic acid amides as prodrugs. Arzneimittel-Forschung, 46(9): 891-894.
25. Jilani, J. A., Pillai, G. K., Salem, M. S., & Najib, N. M. (1997). Evaluation of hydroxyethyl esters of mefenamic acid and diclofenac as prodrugs. Drug development and industrial pharmacy, 23(3): 319-323.
26. Mahfouz, N. M., Omar, F. A., & Aboul-Fadl, T. (1999). Cyclic amide derivatives as potential prodrugs II: N-hydroxymethylsuccinimide-/isatin esters of some NSAIDs as prodrugs with an improved therapeutic index. European journal of medicinal chemistry, 34(7): 551-562.
27. Bandarage, U. K., Chen, L., Fang, X., Garvey, D. S., Glavin, A., Janero, D. R., ... & Tam, S. W. (2000). Nitrosothiol esters of diclofenac: Synthesis and pharmacological characterization as gastrointestinal-sparing prodrugs. Journal of medicinal chemistry, 43(21): 4005-4016.
28. Juntunen, J., Majumdar, S., & Sloan, K. B. (2008). The effect of water solubility of solutes on their flux through human skin in vitro: A prodrug database integrated into the extended Flynn database. International journal of pharmaceutics, 351(1): 92-103.
29. Hirabayashi, H., Sawamoto, T., Fujisaki, J., Tokunaga, Y., Kimura, S., & Hata, T. (2002). Dose-dependent pharmacokinetics and disposition of bisphosphonic prodrug of

diclofenac based on osteotropic drug delivery system (ODDS).Biopharmaceutics & drug disposition, 23(8): 307-315.

30. Dalpiaz, A., Pavan, B., Scaglianti, M., Vitali, F., Bortolotti, F., Biondi, C., ... & Manfredini, S. (2004). Transporter-mediated effects of diclofenac acid and its ascorbyl pro-drug in the in vivo neurotropic activity of ascorbyl nipecotic acid conjugate. Journal of pharmaceutical sciences, 93(1): 78-85.
31. Khan, M. S. Y., & Akhter, M. (2004). Synthesis, biological evaluation and kinetic studies of glyceride prodrugs of diclofenac. Indian journal of experimental biology, 42(11): 1066-1072.
32. Manon, B., & Sharma, P. D. (2009). Design, synthesis and evaluation of diclofenac antioxidant mutual prodrugs as safer NSAIDs. Indian journal of chemistry. Section B, Organic including medicinal, 48(9): 1279.
33. Pathan, A. R., Karwa, M., Pamidiboina, V., Deshattiwar, J. J., Deshmukh, N. J., Gaikwad, P. P., ... & Nemmani, K. V. (2010). Oral bioavailability, efficacy and gastric tolerability of P2026, a novel nitric oxide-releasing diclofenac in rat. Inflammopharmacology, 18(4): 157-168.
34. Borhade, N., Pathan, A. R., Halder, S., Karwa, M., Dhiman, M., Pamidiboina, V., ... & Satyam, A. (2012). NO-NSAIDs. Part 3: nitric oxide-releasing prodrugs of non-steroidal anti-inflammatory drugs. Chemical and Pharmaceutical Bulletin, 60(4): 465-481.
35. Bandgar, B. P., Sarangdhar, R. J., Ahamed, F. A., & Viswakarma, S. (2011). Synthesis, characterization, and biological evaluation of novel diclofenac prodrugs. Journal of medicinal chemistry, 54(5): 1202-1210.
36. Santos, J. L. D., Moreira, V., Campos, M. L., Chelucci, R. C., Barbieri, K. P., Souto, P. C. M. D. C., ... & Chin, C. M. (2012). Pharmacological evaluation and preliminary pharmacokinetics studies of a new diclofenac prodrug without gastric ulceration effect. International journal of molecular sciences, 13(11): 15305-15320.
37. Ghosh, P., Lee, D., Kim, K. B., & Stinchcomb, A. L. (2014). Optimization of Naltrexone Diclofenac Codrugs for Sustained Drug Delivery Across Microneedle-Treated Skin. Pharmaceutical research, 31(1); 148-159.
38. Dhurgham Q. Shaheed, A.K.H.M., Akeel Abdulkadium; Jassim Aboalard, H.K.A., Mohammed Dakhil ALRekabi, and; Husssein, A.H. (2014). Design and synthesis of diclofenac and indomethacin-conjugates with gemcitabine as a possible mutual prodrugs. World Journal of Pharmaceutical Research, 4 (2): 08-17.

39. Suryawanshi, S. B., OSMAN, H. A., Shaikh, Y. I., & NAZERUDDIN, G. (2014). Synthesis of Various Esters of Diclofenac (NSAIDs) as Pro-Drugs and their Biological Evaluation. Chemical Science Transactions, 3(2): 562-565.
40. Bhosle, D., Bharambe, S., Gairola, N., & Dhaneshwar, S. S. (2006). Mutual prodrug concept: fundamentals and applications. Indian journal of pharmaceutical sciences, 68(3): 286.
41. Hasan, S. A., & Elias, A. N. (2014). Synthesis of new Diclofenac derivatives by coupling with chalcone derivatives as possible mutual prodrugs. International Journal of Pharmacy and Pharmaceutical Sciences, 6(1): 239-245.
42. Draganov, D. I., & La Du, B. N. (2004). Pharmacogenetics of paraoxonases: a brief review. Naunyn-Schmiedeberg's archives of pharmacology, 369(1): 78-88.
43. Dahan, A., Khamis, M., Agbaria, R., & Karaman, R. (2012). Targeted prodrugs in oral drug delivery: the modern molecular biopharmaceutical approach. Expert opinion on drug delivery, 9(8): 1001-1013.
44. Moser, V. C., Chanda, S. M., Mortensen, S. R., & Padilla, S. (1998). Age-and gender-related differences in sensitivity to chlorpyrifos in the rat reflect developmental profiles of esterase activities. Toxicological sciences, 46(2): 211-222.
45. Karaman, R., Fattash, B., & Qtait, A. (2013). The future of prodrugs-design by quantum mechanics methods. Expert opinion on drug delivery, 10(5): 713-729.
46. Karaman, R. (2013). Prodrugs Design Based on Inter-and Intramolecular Chemical Processes. Chemical biology & drug design, 82(6): 643-668.
47. Karaman R. Prodrugs for Masking the Bitter Taste of Drugs. (2014). Chapter 12 in Application of Nanotechnology in Drug Delivery, Editor: Ali Demir Sezer, InTech - Open Access Publisher, 399-445.
48. Karaman, R. From Conventional Prodrugs to Prodrugs Designed By Molecular Orbital Methods. (2014) Chapter in Frontiers in Computational Chemistry, Bentham Publisher, 1-77.
49. Karaman, R. (Editor), Prodrugs Design Based On Inter- And Intramolecular Processes, in: Prodrugs Design – A New Era, Karaman, R. editor, Nova Science Publishers, Inc. NY, USA, 2014; 1-76.
50. Abu-Jaish, A.; Jumaa, S.; Karaman, R., Prodrugs Overview , in: Prodrugs Design – A New Era, Karaman R. editor, Nova Science Publishers, Inc. NY, USA, 2014; 77-102.

51. Fattash, B.; Karaman, R., Chemical Approaches Used In Prodrugs Design, in: Prodrugs Design – A New Era, Karaman R. (Editor), Nova Science Publishers, Inc. NY, USA, 2014; 103-138
52. Karaman, R. (2014). Using predrugs to optimize drug candidates. Expert opinion on drug discovery, 9(12): 1405-1419.
53. Karaman, R. (2008). Analysis of Menger's 'spatiotemporal hypothesis'. Tetrahedron Letters, 49(41): 5998-6002.
54. Karaman, R. (2009). Cleavage of Menger's aliphatic amide: a model for peptidase enzyme solely explained by proximity orientation in intramolecular proton transfer. Journal of Molecular Structure: THEOCHEM, 910(1): 27-33.
55. Karaman, R. (2010). The efficiency of proton transfer in Kirby's enzyme model, a computational approach. Tetrahedron Letters, 51(16): 2130-2135.
56. Karaman, R., & Pascal, R. (2010). A computational analysis of intramolecularity in proton transfer reactions. Org. Biomol. Chem., 8(22): 5174-5178.
57. Karaman, R. (2010). A general equation correlating intramolecular rates with 'attack 'parameters: distance and angle. Tetrahedron Letters, 51(39): 5185-5190.
58. Karaman, R. (2011). Analyzing the efficiency of proton transfer to carbon in Kirby's enzyme model—a computational approach. Tetrahedron Letters, 52(6): 699-704.
59. Karaman, R. (2011). Analyzing the efficiency in intramolecular amide hydrolysis of Kirby's N-alkylmaleamic acids–A computational approach. Computational and Theoretical Chemistry, 974(1): 133-142.
60. Karaman, R. (2009). A new mathematical equation relating activation energy to bond angle and distance: a key for understanding the role of acceleration in lactonization of the trimethyl lock system. Bioorganic chemistry, 37(1): 11-25.
61. Karaman, R. (2009). Reevaluation of Bruice's proximity orientation. Tetrahedron Letters, 50(4): 452-456.
62. Karaman, R. (2009). Accelerations in the lactonization of trimethyl lock systems are due to proximity orientation and not to strain effects. Organic Chemistry International, 2009.
63. Karaman, R. (2009). The gem-disubstituent effect—a computational study that exposes the relevance of existing theoretical models. Tetrahedron Letters, 50(44): 6083-6087.
64. Karaman, R. (2009). Analyzing Kirby's amine olefin—a model for amino acid ammonia lyases. Tetrahedron Letters, 50(52): 7304-7309.
65. Karaman, R. (2009). The effective molarity (EM) puzzle in proton transfer reactions. Bioorganic chemistry, 37(4): 106-110.

66. Karaman, R. (2010). Effects of substitution on the effective molarity (EM) for five membered ring-closure reactions–A computational approach. Journal of Molecular Structure: Theochem, 939(1): 69-74.
67. Karaman, R. (2010). The effective molarity (EM) puzzle in intramolecular ring-closing reactions. Journal of Molecular Structure: Theochem, 940(1): 70-75.
68. Menger, F. M., & Karaman, R. (2010). A singularity model for chemical reactivity. Chemistry-A European Journal, 16(5): 1420-1427.
69. Karaman, R. (2010). The effective molarity (EM)–a computational approach. Bioorganic chemistry, 38(4): 165-172.
70. Karaman, R.; Blasko, A.; Almarsson, O.; Arassasingham, R.; Bruice T. C. (1992) Symmetrical and Unsymmetrical Quadruply Aza Bridged Closely-Interspaced Cofacial Bis-5,10,15,20-Tetra-Phenylporphyrins 2.Synthesis, Characterization and Conformational Effects of Solvents. J. Am. Chem. Soc. 114: 4889-4898.
71. Karaman, R. (2010). Proximity vs. strain in intramolecular ring-closing reactions. Molecular Physics, 108(13): 1723-1730.
72. Karaman, R. (2011). The role of proximity orientation in intramolecular proton transfer reactions. Computational and Theoretical Chemistry, 966(1): 311-321.
73. Karaman, R. (2012). Computationally designed enzyme models to replace natural enzymes in prodrug approaches. J Drug Design, 1: e111.
74. Karaman, R. (2013). Prodrug design vs. drug design. J Drug Design, 2: e114.
75. Karaman, R. (2012). The future of prodrugs designed by computational chemistry. Drug Des, 1, e103.
76. Karaman R., Bruice T. C. (1991) Synthesis and Characterization of the First Water Soluble Porphyrin Dimer. J. Org. Chem. 56: 3470-3472.
77. Karaman, R. (2012). Computationally designed prodrugs for masking the bitter taste of drugs. J Drug Design, 1, e106.
78. Karaman, R. (2013). Prodrugs design by computation methods-a new era. Journal of Drug Designing, 1, e113.
79. Karaman, R. (2013). The Prodrug Naming Dilemma. Drug Des, 2, e115.
80. Karaman, R. (2013). A Solution to Aversive Tasting Drugs for Pediatric and Geriatric Patients. Drug Des, 2, e116.
81. Karaman, R. (2011). Analyzing Kemp's amide cleavage: A model for amidase enzymes. Computational and Theoretical Chemistry, 963(2): 427-434.

82. Karaman, R., Ghareeb, H., Dajani, K. K., Scrano, L., Hallak, H., Abu-Lafi, S., ... & Bufo, S. A. (2013). Design, synthesis and in vitro kinetic study of tranexamic acid prodrugs for the treatment of bleeding conditions. Journal of computer-aided molecular design, 27(7): 615-635.
83. Karaman, R., Dajani, K. K., Qtait, A., & Khamis, M. (2012). Prodrugs of Acyclovir–A Computational Approach. Chemical biology & drug design, 79(5): 819-834.
84. Karaman, R., Dajani, K., & Hallak, H. (2012). Computer-assisted design for atenolol prodrugs for the use in aqueous formulations. Journal of molecular modeling, 18(4): 1523-1540.
85. Karaman R, Qtait A, Dajani KK, Abu Lafi S. Design, Synthesis, and In Vitro Kinetics Study of Atenolol Prodrugs for the Use in Aqueous Formulations. The Scientific World Journal, 2014.
86. Karaman, R. (2013). Prodrugs for masking bitter taste of antibacterial drugs—a computational approach. Journal of molecular modeling, 19(6): 2399-2412.
87. Karaman, R. (2011). Computational-Aided Design for Dopamine Prodrugs Based on Novel Chemical Approach. Chemical biology & drug design, 78(5): 853-863.
88. Karaman, R., Dokmak, G., Bader, M., Hallak, H., Khamis, M., Scrano, L., & Bufo, S. A. (2013). Prodrugs of fumarate esters for the treatment of psoriasis and multiple sclerosis—a computational approach. Journal of molecular modeling, 19(1): 439-452.
89. Karaman, R. (2010). Prodrugs of aza nucleosides based on proton transfer reaction. Journal of computer-aided molecular design, 24(12): 961-970.
90. Karaman, R., & Hallak, H. (2010). Computer-Assisted Design of Pro-drugs for Antimalarial Atovaquone. Chemical biology & drug design, 76(4): 350-360.
91. Karaman, R. (2013). Antimalarial Atovaquone Prodrugs Based on Enzyme Models-Molecular Orbital Calculations Approach. Antimalarial Drug Research and Development, Banet, A C. & Brasier, P. Ed, 1-67.
92. Karaman, R., Fattash, B., Mecca, G., & Bader, M. (2014). Computationally designed atovaquone prodrugs based on Bruice's enzyme model. Current computer-aided drug design, 10(1): 15-27.
93. Karaman, R., Amly, W., Scrano, L., Mecca, G., & Bufo, S. A. (2013). Computationally designed prodrugs of statins based on Kirby's enzyme model. Journal of molecular modeling, 19(9): 3969-3982.

94. Karaman, R., Karaman, D., & Zeiadeh, I. (2013). Computationally-designed phenylephrine prodrugs–a model for enhancing bioavailability. Molecular Physics, 111(21): 3249-3264.
95. Khawaja y., Karaman, R. (2015). A Novel Mathematical Equation for Calculating the Number of ATP Molecules Generated From Sugars in Cells. World Journal of Pharmaceutical Research, 4(4): 303-312.
96. Karaman R. (2015). Design of Prodrugs to Replace Commonly Used Drugs Having Bitter Sensation. World Journal of Pharmaceutical Research, 4(2): 49-58.
97. Hejaz, H., Karaman, R., & Khamis, M. (2012). Computer-assisted design for paracetamol masking bitter taste prodrugs. Journal of molecular modeling, 18(1): 103-114.
98. Abu-Jaish, A.; Mecca, G.; Jumaa, S.; Thawabteh, A.; Karaman, R. (2015) Mefenamic acid Prodrugs and Codrugs- Two Decades of Development. World Journal of Pharmaceutical Research 4(6): 2408-2429.
99. Karaman, R. (2015) Computationally Designed Prodrugs Based on Enzyme Models" Aperito Journal of Drug Designing and Pharmacol 2015; 2: 111. http://dx.doi.org/10.14437/AJDDP-2-111.